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**Kinetic and Mechanistic Studies on Some
One-Electron and Two-Electron Reactions**

by

Darren William Snelgrove

A thesis submitted in
partial fulfillment of the requirements for the
Degree of Doctor of Philosophy

to

The Faculty of Graduate Studies and Research

Department of Chemistry

Carleton University

Ottawa, Canada

May, 2000

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The Faculty of Graduate Studies and Research
acceptance of this thesis

**Kinetic and Mechanistic Studies on Some
One-Electron and Two-Electron Reactions**

Submitted by
DARREN WILLIAM SNELGROVE, B. Sc.
in partial fulfillment of the requirements for
degree of Doctor of Philosophy

Department Chair

Thesis Supervisor

External Examiner

Carleton University
2000

Abstract

The initial focus of the work described in this thesis was to provide simple methods to distinguish between radical and non-radical mechanisms of hydrocarbon oxidations that use *tertiary* alkyl hydroperoxides as the oxidant and a metal catalyst. The first part of this thesis describes how 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH) can be used to distinguish between radical and non-radical mechanisms. Using a Ti(IV) catalyst on a silica support and cyclohexene it was demonstrated that MPPH is a highly effective 2-electron oxidant surpassing *tert*-butyl hydroperoxide (TBHP) in epoxidation of this alkene. This was important since it demonstrates that MPPH can be used as a mechanistic probe to discriminate between one and two electron oxidations of hydrocarbons. In addition, it was found that the difference in hydrophobic / hydrophilic nature of alcohols produced in the epoxidation process from the two hydroperoxides, MPPH and TBHP, which makes the former a better epoxidizing agent.

Phenols are highly efficient radical traps, which makes them potential probes for distinguishing between radical and non-radical hydrocarbon oxidation mechanisms. However the kinetics of the radical / phenol reaction must be known in order for phenols to be used effectively as mechanistic probes. This is *not* trivial because radical / phenol reactions are subject to kinetic solvent effects. In the second and major part of my thesis an equation is developed that allows rate constants to be reliably and accurately predicted for a $RXH/Y^{\bullet}$ reaction in over 250 solvents based one rate constant and two empirical parameters. One parameter, β_2^H , is a relative measure of a solvents ability to accept a hydrogen bond, the other, α_2^H , is a relative measure of the ability of a substrate (the H-atom donor) to donate a hydrogen bond. This equation is given by

$$\log k_{RXH/Y^{\bullet}}^S = \log k_{RXH/Y^{\bullet}}^o - 8.3(\alpha_2^H \cdot \beta_2^H).$$

This equation was found general for phenols –regardless of the substituents– alkyl hydroperoxides, anilines and alkanes, which led to the conclusion that the equation is general for all substrates. In addition, if two rate constants are known for a $ArOH/Y^{\bullet}$ reaction for two non-sterically hindered phenols in any solvent (or solvents) then the rate constant for any other phenol (non-sterically hindered) can be predicted in any solvent using the same equation and Brown and Okamoto's σ^+ parameter

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As a graduate student of Carleton University working at the National Research Council on Sussex Dr. I had the privilege of working with many talented scientists. I am grateful to Dr. Philip MacFaul, who was my first mentor at the NRC, for his thoughtful assistance and guidance. I would like to acknowledge Dr. Jeff Banks for helping me get started on the Kinetic Solvent Effect project, as well as, Professor Peter Mulder for many fruitful discussions and a most rewarding collaboration. Gratitude is extended to my good friend Dr. Deepak Shukla for the insightful conversations and encouragement. I would like to express thanks to Dr. Thomas Paul for his helpful advice and companionship in the lab and at the pub. I would like to acknowledge special friendships made during my studies at the NRC, Dr. Mary Jane Young, Dr. David Hall, and Leanne Bedard.

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1 Hydrocarbon oxidation

1.1 Introduction:

The selective functionalization of alkanes has long been a tantalizing challenge for organic chemists. Their low price and great abundance makes alkanes ideal feed stock for many industrial syntheses.¹ However, the inert nature of saturated hydrocarbons makes them among the most difficult organic compounds to oxidize. For example, the oxidation of cyclohexane to cyclohexanol and cyclohexanone is an important commercial reaction, providing about one million tons of the oxidized hydrocarbon per year for its conversion into caprolactam and ultimately, to nylon.² Typically, cyclohexane has been oxidized under high pressure air using a cobalt(II) catalyst. Although the reaction is run to only a low percent conversion (ca. 5%), the desired products are obtained with a selectivity of only eighty-five percent. The desired and undesired products must be separated from each other and from the large amount of un-reacted cyclohexane by fractional distillation. The preferred products are further processed while the cyclohexane is returned to the reactor. By way of contrast, nature has evolved a number of enzymes, which can perform the conversion of saturated hydrocarbons to the corresponding alcohols with a high selectivity and under very mild conditions. These enzymes are called oxygenases.

1.2 Oxygenases

Two iron-based groups of biological catalysts, methane monooxygenases (MMO) and cytochrome P-450's (P-450) have received a great deal of attention because they can oxidize alkanes to alcohols using dioxygen from the air as the oxidant. Although these

two classes of enzymes have very different catalytic sites^{3,4} they perform similar functions. In MMO this site consists of a μ -oxo-bridged binuclear iron center in a nonheme environment,^{3,5} whereas in P-450 this site is a mono-iron heme protoporphyrin [IX].⁴ The mechanism of alkane hydroxylation by MMO and P-450 are surprisingly similar considering that the iron is present at the active sites of these two enzymes with such different ligands.⁶⁻⁸

Mechanistic studies of alkane hydroxylation by P-450 and P-450 model catalysts indicate that the reaction proceeds via the catalytic cycle shown in Scheme 1.1.^{4,9} The cycle begins from the resting state of the mono-nuclear Fe (III) (top left of Scheme 1.1) with the reversible binding of the substrate, SH, to the enzyme. This is followed by an irreversible one electron reduction of the Fe (III) to Fe (II) (three o'clock in Scheme 1.1), the reducing equivalents being furnished by either NADH or NADPH, and then by the reversible binding of molecular oxygen. One electron reduction of the iron-peroxo species and the addition of two protons leads to a heterolytic cleavage of the O-O bond with loss of water and generation of the active oxidant (seven-thirty in Scheme 1.1). It is believed that the active oxidant is an iron (IV) oxene with the fifth oxidizing equivalent present on the porphyrin ring as a delocalized radical cation i.e., $[\text{Fe}^{\text{IV}}=\text{O}]^{\bullet+}$, which can be formally represented as $\text{Fe}^{\text{V}}=\text{O}$. Lastly, a two-electron oxidation of the substrate and two-electron reduction of the catalyst produces the hydroxylated product and regenerates the resting ferric state of the enzyme.

Scheme 1.1. Catalytic cycle for the oxidation of a substrate, SH , to its alcohol, SOH , by of cytochrome P-450. Only the iron of the P-450 is shown.

The iron (III) protoporphyrin cofactor is also present in various peroxidases and in catalase. The peroxidases can carry out the same type of oxygen insertion into carbon-hydrogen bonds as the P-450's. However, these enzymes dispense with the direct need for a sacrificial reductant (such as NADH or NADPH) by using 2e-reduced dioxygen in the form of hydrogen peroxide or an organic hydroperoxide. Monooxygenases can also insert oxygen into C-H bonds, without a reducing agent, in the presence of hydrogen peroxide or alkyl hydroperoxides. This pathway is called the peroxide shunt and is shown in Scheme 1.1.^{8,10}

1.2.1 Biomimetic Catalytic Systems:

The use of model compounds to emulate enzymes is an important approach to understanding the mechanisms of biological processes including the activation of hydrocarbons and dioxygen.^{4,5} Biomimetic non-heme iron systems have, for simplicity, generally attempted to mimic enzyme / hydroperoxide systems, i.e., to follow the peroxide shunt (Scheme 1.1) by using a sacrificial oxygen atom donor (such as *tert*-butylhydroperoxide) rather than dioxygen plus a sacrificial reductant such as NADPH.¹¹

1.2.1.1 Gif Chemistry

Several research groups have developed a variety of iron-based catalytic chemical systems that have been claimed to imitate the oxygenases. Among the more important of these are the late Professor D. H. R. Barton's numerous "Gif" systems.¹²⁻¹⁴ Most of the Gif systems use an inorganic Fe (III) salt together with picolinic acid and either hydrogen peroxide or *tert*-butyl hydroperoxide as the oxygen atom source in a solution of pyridine and acetic acid.¹² The general mechanism proposed for these oxidations involved the

Scheme 1.2. Professor Barton's proposed catalytic cycle for Gif chemistry (X=H or Me₃C). Products are shown in bold face.

formation of an $\text{Fe}^{\text{V}}=\text{O}$ species which inserted into a (generally unactivated) carbon-hydrogen bond to form an intermediate containing an iron-carbon bond, as shown in Scheme 1.2. Dioxygen was then assumed to insert into the iron-carbon bond and subsequent reactions lead to the oxidized products which are, for the most part, ketones and alcohols.¹⁴

1.2.1.2 Que Chemistry

Professor L. Que, Jr., has developed another important group of iron-based, purported biomimetic alkane oxidation systems. He has characterized numerous iron complexes containing the tripodal tris(pyridinylmethyl) amine (TPA) ligands. These include both mono-iron (III) complexes, e.g., $[\text{Fe}^{\text{III}}\text{Cl}_2(\text{TPA})]^+$ and μ -oxo di-iron (III) complexes, e.g., $[\text{Fe}_2(\text{TPA})_2\text{O}(\text{OAc})]^{3+}$.^{15,16} These catalytic systems were reacted with *tert*-butyl hydroperoxide (TBHP, usually 140 equivalents based on 0.7mM catalyst), and an excess of cyclohexane (0.77 M) in acetonitrile under an atmosphere of argon at room temperature. The products were cyclohexanol, cyclohexanone and cyclohexyl *tert*-butyl peroxide which were formed in a roughly 1:1:1 ratio in more than stoichiometric quantities (based on catalyst).

The proposed mechanism starts with the heterolytic bond cleavage of the O-O bond to yield a high-valent iron-oxo species, similar to that which Barton had proposed, see Scheme 1.3.¹⁷ However, the subsequent reactions proposed by Que differ from those of Barton in that no iron-carbon bonded species $\text{Fe}^{\text{V}}\text{-R}$ was suggested. Hydrogen atom abstraction by the iron oxene ($\text{Fe}^{\text{V}}=\text{O}$) was supposed to afford the cyclohexyl radical following which, a Groves type of “in-cage” oxygen rebound occurred to yield the

Scheme 1.3: Proposed mechanism of hydrocarbon oxidation by [Fe(III)TPA] catalyst with TBHP.

cyclohexanol product.¹⁴ It is noteworthy that cyclohexyl chloride was also identified and the same in-cage “rebound” mechanism was proposed except that the alkyl radical abstracts the chlorine ligand.

1.2.2 Biomimetic Systems vs. Oxygenases

Claims by Barton, Que, and others for alkane oxidations which do not involve freely diffusing radicals rest on the assumption that their biomimetic catalysts generated reactive high-valent, iron-oxo species (Scheme 1.2 and 1.3), formally $[\text{Fe}=\text{O}]^{\text{V}}$. The intermediate ($[\text{Fe}=\text{O}]^{\text{V}}$) is formed by the heterolytic cleavage of the O-O bond in the hydroperoxide, XOOH. All these purported examples of alkane oxidation via biomimetic high-valent iron-oxo species yielded complex mixtures of oxidation products. For example, with cyclooctane as the substrate and *tert*-butyl hydroperoxide as the oxidant the major products identified have been cyclooctanone, cyclooctanol, and the mixed peroxide, cyclooctyl *tert*-butyl peroxide. Such product mixtures are certainly not reminiscent of enzyme chemistry, which will normally yield a single product. It would seem that these reactions appeared biomimetic only in the eyes of their inventors!

1.2.3 Alkane Oxidation Mediated by Free-Radicals:

The observed product mixtures in both the Gif and Que systems can be easily accounted for by simple and well-understood free radical chemistry (Scheme 1.4) in which freely diffusing radicals are produced by the *homolytic* cleavage of the O-O bond. According to Scheme 4 the first step in the catalytic cycle is the homolytic cleavage of the O-O bond in TBHP to give a *tert*-butoxyl radical and an iron (IV) complex, reaction 1.

Scheme 1.4. The radical route to the products observed for the oxidation of cyclohexane by TBHP, catalyzed by Fe (III) in pyridine/glacial acetic acid, at room temperature. Identified products are shown in bold face.

The Fe (III) catalyst is regenerated (reduced back to Fe(III)) by the subsequent oxidation of another TBHP to yield a *tert*-butylperoxyl radical, reaction 2. The observed products are then easily accounted for by the reactions following the formation of the freely diffusing *tert*-butoxyl and peroxyl radicals.

1.3 Probing the Mechanism of Alkane Oxidation.

1.3.1 Oxidants as Mechanistic Probes

The involvement of free-radicals in purported non-radical, biomimetic oxidations has generally been demonstrated by product analysis in experiments designed to produce predictable changes in the nature of the products, or in their relative (or absolute) yields.¹⁸⁻²⁰

One general method to distinguish between reaction mechanisms mediated by free radicals and those controlled by high valent iron-oxo intermediates is to change the tertiary hydroperoxide in such a way that the intrinsic lifetime, τ , of the corresponding alkoxyl radical would be much shorter than that of *tert*-butoxyl radical. The intrinsic lifetime is the reciprocal of the first-order rate constant for alkoxyl radical decay in the absence of substrate but in the solvent and at the temperature at which the alkane oxidations are carried out. The intrinsic lifetime of an alkoxyl radical will be reduced if it undergoes either a more facile β -scission than *tert*-butoxyl radical or a rearrangement not available to *tert*-butoxyl. Both of these strategies will convert the reactive *tert*-alkoxyl radical into a relatively unreactive carbon-centered radical. The intrinsic lifetime for *tert*-butoxyl radicals ($R=CH_3$) in acetonitrile at 298 K is $\tau = 12\mu s$ (i.e., $k_\beta = 8.3 \times 10^4 s^{-1}$).

The rate constant for hydrogen atom abstraction by *tert*-butoxyl radicals from cyclohexane is solvent independent: $k_H = 1.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.²¹

Thus, for a solution of 1 M of cyclohexane in acetonitrile the relative rate of hydrogen abstraction to β -scission is:

$$\frac{k_H}{k_\beta} [\text{C}_6\text{H}_{12}] = \frac{1.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1} \times 1.0 \text{ M}_{\text{C}_6\text{H}_{12}}}{8.3 \times 10^4 \text{ s}^{-1}} = 14.5 \quad (1.15)$$

Thus, the majority of *tert*-butoxyl radicals will react with the cyclohexane. However, if the alkoxyl radical lifetime is sufficiently reduced, i.e., $\tau_{\text{RC}(\text{CH}_3)_2\text{O}\cdot} \ll \tau_{\text{C}(\text{CH}_3)_3\text{O}\cdot}$, there can be no reaction of $\text{RC}(\text{CH}_3)_2\text{O}\cdot$ with the cycloalkane.

The *tert*-alkoxyl radical derived from 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH) is very short-lived because the corresponding alkoxyl radical undergoes an extremely rapid β -scission, $k_\beta = 2.2 \times 10^8 \text{ s}^{-1}$.²⁰ This reaction is, in fact, too rapid for there to be any significant hydrogen atom abstraction from a saturated hydrocarbon. For example, if this radical were to be generated in a solution containing 1M cyclohexane:

$$\frac{k_H}{k_\beta} [\text{C}_6\text{H}_{12}] = \frac{1.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1} \times 1.0 \text{ M}_{\text{C}_6\text{H}_{12}}}{2.2 \times 10^8 \text{ s}^{-1}} = 5.5 \times 10^{-3}$$

This means for every 200 alkoxyl radicals generated only 1 will abstract a hydrogen atom from the cyclohexane, the other 199 will undergo a rearrangement via β -scission to give benzyl radicals (Scheme 1.5) which will furnish “signature” products, viz., bibenzyl, benzyl alcohol, and benzaldehyde (Scheme 1.6). By using MPPH in place of TBHP the formation of, or the absence of products derived from, the benzyl radical enables a researcher to determine whether alkoxyl radicals were intermediates in the reaction under investigation.

Scheme 1.5. Generation of the alkoxyl radical from MPPH and the fate of the oxygen centered radical.

Scheme 1.6. "Signature" products expected to be derived from the benzyl radical of MPPH.

Similarly, when MPPH is used as the oxidant the formation or the absence of oxidation products derived from added hydrocarbons such as cyclohexane enables a distinction to be made between two mechanisms, one involving freely diffusing radicals and the other a non-radical mechanism.

Since all tertiary alkyl hydroperoxides should yield the same high-valent, iron-oxo species, MPPH would be expected to give the same products as TBHP, if the hydroperoxides' O-O bond undergoes heterolytic cleavage (as proposed by Barton and Que). However, in the GoAgg^V system, for example, and with cyclooctane as substrate TBHP gave cyclooctanone, cyclooctanol, and cyclooctyl *tert*-butyl peroxide, whereas MPPH gave benzaldehyde, benzyl alcohol and bibenzyl (Scheme 1.6) and essentially no cyclooctane oxidation products.¹⁸ This difference between TBHP and MPPH is most easily explained in terms of the lifetimes of the corresponding *tert*-alkoxyl radicals, viz., 12 μ s and 5ns, respectively, and indicates that the reaction occurs by a free-radical mechanism.

Despite the simplicity of the alkoxyl radical lifetime-based explanation, both implicit²² and explicit^{23,24} arguments were made that MPPH was not a competent substitute for TBHP and that this probe was predisposed to radical chemistry in the iron-catalyzed systems, e.g., reaction 1.16.

Another, major criticism of the MPPH probe was that there were no reported successful oxidations of hydrocarbons using this hydroperoxide. I thought that the failure of MPPH to oxidize hydrocarbons was more likely due to the fact that the reactions in all the systems tested actually involved free-radicals rather than the proposed high-valent iron oxene [$\text{Fe}^{\text{V}}=\text{O}$]. That is, I thought that the systems tested all involved 1-electron oxidations and not the 2-electron oxidation of genuine monooxygenase mimics.

1.3.2 Traps for Oxygen Centered Radicals

One method of looking for alkoxyl radical intermediates in a reaction involving *tert*-alkyl hydroperoxides is to use MPPH. An alternate method which is more general and is an equally powerful diagnostic tool for alkoxyl radicals is to use certain additives which preferentially react with (i.e., trap) alkoxyl radicals if they are, indeed, involved in the reaction. The great advantage of the alkoxyl radical trap technique is that the normal reaction conditions for the system of interest are maintained but the reaction pathway is changed in a manner, which can, ideally, be precisely predicted. The concept underlying the use of a chemical trap (or probe) for a free radical reactive intermediate is generalized below.

Scheme 1.7. Schematic diagram demonstrating how reactive intermediates may be trapped to alter the normal reaction pathway.

Consider the reaction of $A^\bullet$ with compound B;

to which is added a suitable probe (P) which is known to be a trap for $A^\bullet$:

Now, it is commonly, *but incorrectly*, assumed that if P does not change the normal reaction pathway, then $A^\bullet$ must be absent. This conclusion is without justification unless the kinetics, of all relevant reactions in the system, are *well understood*. Additive P can only provide an insight into the mechanism of the reaction, which converts B to D if, the $A^\bullet + P$ reaction (1.18) competes effectively with the $A^\bullet + B$ reaction (1.17). This requires knowledge of the rate constants for reactions 1.17 and 1.18. Only then can the appropriate concentration of P be employed and, indeed, the choice of P provide useful mechanistic information. The partitioning of $A^\bullet$ between reactions 1.17 and 1.18 is given by:

$$\frac{k_P \times [P]}{k_B \times [B]} = \frac{[\text{products derived from P}]}{[\text{products derived from B}]}$$

Useful mechanistic information can only be obtained if $k_P [P] > k_B [B]$ because only then will the normal reaction pathway be significantly affected, and if $k_P [P] \gg k_B [B]$ the normal reaction pathway will be closed down completely.

1.3.2.1 Antioxidants as Radical Traps

Antioxidants such as phenols (ArOH) are excellent traps for alkoxyl and peroxy radicals. They have been used both properly and, perhaps even more commonly, improperly to probe for the reactive intermediates involved in iron-catalyzed alkane oxidations using hydroperoxides as oxidants.

2,6-Di-*tert*-butyl-4-methylphenol, (BHT, butylated hydroxytoluene) is the major phenolic antioxidant used commercially to stabilize oils, greases, rubbers and polymers against oxidative degradation. Not surprisingly, it has therefore also been an extremely popular probe for identifying the reactive intermediates responsible for alkane oxidation with various iron(III) catalysts used in conjunction with TBHP. As one example (and cautionary tale), 15 mM of BHT was added to a system comprising catalyst (0.7 mM), cyclohexane (0.77), and TBHP (3.5 mM) in *acetonitrile*.¹⁷ There was no inhibition of product (cyclohexanol, cyclohexanone, cyclohexyl *tert*-butyl peroxide) formation from which it was concluded that alkoxyl radicals were not involved in the reaction and that the mechanism was a non-radical, 2-electron oxidation process. That is, it was concluded that the reaction emulated P-450 chemistry and was therefore biomimetic. However, consider the actual situation and the competition between cyclohexane and BHT for any alkoxyl radical (Scheme 1.9).

Scheme 1.9. Competitive reaction between cyclohexane and the antioxidant BHT for the alkoxyl radical ($\text{RO}\bullet$).

i) cyclohexane 0.77M

$$k_H \times [\text{C}_6\text{H}_{12}] = 1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1} \times 0.77 \text{ M} = 7.7 \times 10^5 \text{ s}^{-1}$$

ii) BHT 15 mM

$$k_{\text{BHT}} \times [\text{BHT}] = 2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1} \times 0.015 \text{ M} = 3 \times 10^5 \text{ s}^{-1}$$

Therefore, if alkoxyl radicals were involved one could expect no more than a modest decrease in product yields. This may actually have occurred but yields and the ability to reproduce these yields was not reported! It is certain that insufficient BHT was employed to draw any meaningful mechanistic conclusions. These would have required experiments at several (higher) concentrations of BHT and a proper kinetic analysis.

As a more positive example of the use of antioxidants to probe reaction mechanisms MacFaul and coworkers¹⁹ used two different antioxidants, namely: BHT and diphenylamine, to examine Sawyer's "oxygenated Fenton chemistry"²⁵. This is another purported example of non-radical hydrocarbon oxidation claimed to involve a high-valent iron-oxo species. Several different concentrations of the two antioxidants were used together with three substrates and four of Sawyer's iron-based catalysts. It was demonstrated that the yields of alkane oxidation products were reduced exactly as would be predicted from the kinetics of the reactions of the alkoxyl and peroxy radicals with the three substrates and with BHT or diphenylamine. Clearly "oxygenated Fenton chemistry" is yet one more example of free-radical chemistry not biomimetic oxygenase chemistry.

1.4 The Thesis

1.4.1 Can MPPH Distinguish 1 and 2 Electron Oxidations?

The tertiary alkyl hydroperoxide, 2-methyl-1-phenyl-2-propylhydroperoxide (MPPH) has been used by myself^{11,18} and others at the NRC^{19,20,26} to study the mechanism of saturated hydrocarbon oxidation by *tert*-alkyl hydroperoxides catalyzed by iron salts and porphyrins. In all cases, the results indicated that the hydrocarbon oxidations involved freely diffusing alkoxyl radicals, which was contrary to the P-450 like mechanisms that had been proposed. However, there were no reports of successful oxidations using MPPH. If MPPH is really to be a valid mechanistic probe for hydrocarbon oxidations using alkyl hydroperoxides and metal catalysts it had to be demonstrated that it is, indeed, capable of performing authentic two electron oxidations.

Ti(IV) on a silica support selectively catalyses the epoxidation of alkenes by *tert*-butyl hydroperoxide. Although several mechanisms have been proposed for the oxidation, none involve free radicals, rather they involve an “oxygen insertion” type mechanism. Using Ti(IV) catalysts I was able to show that MPPH is capable of oxidizing olefins to epoxides, and thus is suitable replacement for *tert*-butyl hydroperoxide in studies of the mechanisms of hydrocarbon oxidations.

1.4.2 Predicting Rate Constants for Phenol / Radical Reactions

It will be clear that the use of antioxidants to investigate the mechanism of alkane oxidations is an extremely powerful and useful technique provided the absolute constants for all the potentially relevant reactions of alkoxyl and peroxy radicals are known. This is not a trivial requirement considering that there have been relatively few relevant kinetic measurements. This paucity of relevant kinetic data is further augmented by the fact that there have been several reports indicating that hydrogen atom abstraction by oxygen-centered radicals from, at least, some phenols, are strongly solvent dependent.^{27,28} Most of the purported {ButOOH / Fe (III) / RH} biomimetic systems have employed somewhat unusual solvents e.g., pyridine, pyridine / acetic acid, and pyridine / acetonitrile mixtures. There is absolutely no kinetic data pertaining to alkoxyl radical / phenol reactions in such solvent systems.

In order for phenols to be truly useful as mechanistic probes for alkoxyl radical-mediated chemical reactions it is necessary to know the rate constants for alkoxyl radical trapping. Because of kinetic solvent effects (KSE) the rate constants- for reactions 1.19 and 1.20- must be measured for each phenol in each solvent. Obviously it would be beneficial if the magnitude of k_H , (reaction 1.19 and 1.20) could be reliably predicted for any phenol in any solvent or solvent mixture, based on the physical properties of the phenol and the solvent. The search for and the discovery of a general equation which allows such predictions is the main topic of my thesis. In achieving the ability to predict the rate constants for hydrogen atom abstraction by alkoxyl radicals (reaction 1.19) from meta and para (and even some ortho) substituted phenols in any pure solvent or solvent mixture, I found that I could also predict the rate constants for abstraction of the phenolic

hydrogen atom from phenols by other radicals provided I had one or two rate constants for the other radical. In fact, I will show that rate constants can be reliably predicted in any solvent for any phenol / radical reaction based on one rate constant for the reaction of interest in any solvent. Moreover, for a “*new*” radical, a measured rate constant (in any solvent) for each of two different phenols –preferably one with an electron donating, and one with an electron withdrawing substituent– I have found that the rate constants can be accurately predicted for all sterically non-hindered phenols in any solvent. Thus, my Ph.D. work has given chemists the ability to predict many thousands of rate constants for abstraction of phenolic hydrogen atom with remarkably high precision and great simplicity. This predictive ability extends to non-hydroxylic substrates as well.

2 Epoxidation of Alkenes Catalyzed by Ti(IV)

2.1 Introduction

I,^{11,18} as well as others,^{19,20,26} have made extensive use of 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH), in place of *tert*-butyl hydroperoxide (TBHP)), to demonstrate that numerous claims for non-free radical, two-electron cyclohexane oxidations using TBHP and various iron-based catalysts actually occurred via normal free radical chemistry. It was suggested that MPPH was not a competent replacement for TBHP in Fe / hydroperoxide / cyclohexane systems; i.e., in these purported two-electron oxidation processes.²²⁻²⁴ In other words, it was suggested that MPPH was not capable of performing genuine two-electron alkane oxidations. To address this concern I decided to use MPPH in reactions which gave every appearance of being authentic two-electron oxidations.

Because of the industrial importance of epoxides, there has been a great deal of research on metal-catalyzed epoxidations of alkenes.²⁷ Generally these systems use hydroperoxides to provide the necessary oxygen atom.

2.1

I decided to study the titanium (IV)-catalyzed epoxidation of alkenes by alkyl hydroperoxides, specifically MPPH and TBHP.

A titanium (IV) catalytic system was selected because there are some data to indicate that the mechanism of alkene epoxidation in Ti (IV) / ROOH / *c*-C₆H₁₀ systems is non-radical, and that it is, indeed, an authentic two electron oxidation. ^{1,27-30} Examples of proposed mechanisms are shown below.

In this study I used a heterogeneous catalyst in which the catalytically active titanium is incorporated in mesoporous SiO₂ (MCM-41). MCM-41 is a non-crystalline powder synthesized from silica using micells as a template. Unlike zeolites, MCM-41 is comprised of only silica and its structure is not highly ordered.

Interest in Ti(IV)-catalyzed epoxidations of alkenes has recently intensified, because Ti(IV)-containing mesoporous MCM-41 silicas with their large pore apertures

(typically 30 Å) are capable of oxidizing relatively bulky substrates.³¹ Two distinct kinds of Ti (IV) modified MCM-41 epoxidation catalysts have been described.

The first (Ti→MCM 41) accommodates the titanium ions within the walls of the mesoporous silica. The second (Ti↑MCM 41) has the tetracoordinated Ti (IV) ions grafted onto the inner surfaces of the mesoporous host, as shown above. Ti(IV) catalyzed alkene epoxidations using TBHP as the oxidant occur very cleanly with by-product formation being minor. Cyclohexene was oxidized using TBHP and the MCM-41 Ti(IV) catalysts. The procedure was repeated with MPPH to determine if this hydroperoxide is capable of two-electron oxidations (if that really is the mechanism of epoxidation).

2.2 Results and Experimental

2.2.1 Cyclohexene Epoxidation

Cyclohexene (0.5 mL, 4.9 mmol) was oxidized in the presence of the two titanium catalysts (75 mg) and the *tert*-alkyl hydroperoxide (5.0 mmol) in acetonitrile (8 mL). The reaction was stopped after one hour by the addition of triphenylphosphine (1.5 g, 5.7 mmol) which quantitatively converts the hydroperoxide to the corresponding alcohol.

All experiments were performed under argon unless stated otherwise.

2.2.2 Catalyst

The catalysts used in the present study were prepared according to the literature,^{32,33} and were not handled in any special manner after calcination at 550 °C for 4h under oxygen. The Si : Ti ratios for Ti→MCM 41 and Ti↑MCM 41 were 1 : 0.058 and 1 : 0.041 respectively.

2.2.3 Product Analysis

Products were analyzed by GC/MS and GC/FID using a HP Ultra-2 column (dimensions: 12m x 0.2mm x 0.33μm film thickness). The temperature program was as follows: 50 °C for 5 min, 8 °C /min to 250 °C, 250 °C for 5 min. Products were identified by comparisons of reaction products (MS and retention times) with authentic standards. Analytes were quantified using 1,4-dibromobenzene as an internal standard and GC/FID.

Table 2.1. Cyclohexene epoxidation at 25°C in acetonitrile under argon using *tert*-butyl hydroperoxide as the oxidant. Two numbers separated by a comma indicate the results of duplicate experiments.^a

No.	Catalyst	Cyclohexene Oxide [%] ^{b,c}	Other products [%] ^{c,d}	Selectivity w.r.t. the epoxide [%] ^e	Turnover frequency h ⁻¹ ^f
1	Ti↑MCM41	13.5, 12.4	0.7, 0.2	95.2, 98.7	16.4, 15.3
2	Ti→MCM41	1.8, 1.5	0.1, 0.1	94.4, 94.7	1.5, 1.3
3	MCM41	0.0	0.7 ^g	0.0	-
4	UV light	0.3	9.6 ^h	2.5	-
5	Ti↑MCM41 ⁱ	0.1	0.1	ca. 50	<0.1

^a Cyclohexene (0.5 mL, 4.9 mmol), catalyst (75 mg), *tert*-butyl hydroperoxide (5.0 mmol), acetonitrile (8 mL). ^b Percentages given are based on the amount of cyclohexene converted into cyclohexene oxide. ^c The errors are estimated to be $\pm(0.03) \times (\% \text{ analyzed product})$. ^d Other products derived from cyclohexene. ^e Based on cyclohexene derived products. ^f Number of moles of epoxide per mole of Ti^{IV} per hour. ^g Only cyclohexenol detected. ^h Cyclohexenol (6.6%), cyclohexenone (1.0%), and *tert*-butyl cyclohexenyl peroxide(1.9%). ⁱ The catalyst was pretreated with TBHP and washed before the addition of cyclohexene.

It can be seen from entries 1 and 2 in Table 2.1, that using TBHP cyclohexene epoxidation can occur with an excellent selectivity. Furthermore, by comparing these two entries, it can be seen that the catalyst with the Ti(IV) on the silica surface, Ti↑MCM41, is roughly ten times as active per Ti^{IV} as the catalyst with the Ti(IV) embedded throughout the silica, Ti→MCM41.

Entry 3 demonstrates that the active catalyst is the titanium incorporated onto, or into the mesoporous MCM41 silica framework, since MCM41 without titanium did not yield any oxidation products.

I repeated my experiments using MPPH in place of TBHP. It proved to be an even more effective epoxidizing agent than TBHP (cf. Table 2.1 with Table 2.2).

Table 2.2. Cyclohexene epoxidation in acetonitrile at 25°C under argon using MPPH as the oxidant. Two numbers separated by a comma indicate the results of duplicate experiments.^a

No.	Catalyst	Cyclohexene Oxide [%] ^{b,c}	Other products [%] ^{c,d}	Selectivity w.r.t. the epoxide [%] ^e	Turnover frequency h ⁻¹ ^f
1	Ti↑MCM41	36.3, 23.5	0.3, 0.4	99.2, 99.0	37.3, 28.9
2	Ti→MCM41	3.3, 3.2	0.5, 1.8	88.3, 73.6	2.5, 2.7
3	MCM41	0.0	0.0	0.0	-
4	UV light	0.1	28.6 ^g	0.3	-
5	Ti↑MCM41 ^h	0.0	0.0	0.0	-

^a Cyclohexene (0.5 mL, 4.9 mmol), catalyst (75 mg), MPPH (5.0 mmol), acetonitrile (8 mL). ^b Percentages given are based on the amount of cyclohexene converted into cyclohexene oxide. ^c The errors are estimated to be $\pm(0.03) \times (\% \text{ analyzed product})$. ^d Other products derived from cyclohexene. ^e Based on cyclohexene derived products. ^f Number of moles of epoxide per mole of Ti^{IV} per hour. ^g Cyclohexenol (11.3%), benzyl alcohol (7.5%) and bibenzyl (9.8%). ^h The catalyst was pretreated with MPPH and washed before the addition of cyclohexene.

To my knowledge, this is the first time that MPPH has been demonstrated to be an effective oxidant. It gives a two to three-fold higher yield of epoxide than TBHP and with little (Ti→MCM41) or no (Ti↑MCM41) loss of selectivity. Again the Ti↑MCM41 catalyst was about an order of magnitude more active than the Ti→MCM41 catalyst. Cyclohexene does furnish some cyclohexene oxide when it is oxidized under free radical conditions with TBHP (Scheme 2.1). However, this epoxide is formed in relatively low amounts compared with the yield of cyclohexenol, cyclohexenone, and the mixed peroxide, *tert*-butyl cyclohexenyl peroxide, Table 2.3. Moreover, when MPPH was used under free radical conditions in place of TBHP, “signature” products derived from benzyl radicals were detected, viz., bibenzyl, and benzyl alcohol (Scheme 1.6).

Table 2.3. Products from reactions initiated by UV irradiation in the presence of a *tert*-alkyl hydroperoxide and cyclohexene under an atmosphere of argon ^a

No.		Cyclohexene Oxide ^b	Cyclo- hexenol ^b	Cyclo- hexenone ^b	Mixed peroxide ^b	Bibenzyl ^b	benzyl alcohol ^b
1	TBHP	0.3	6.6	1.0	1.9	N/A ^c	N/A ^c
2	MPPH	0.1	11.3	N.D. ^d	N.D. ^d	9.8	7.5

^a Cyclohexene (0.5 mL, 4.9 mmol), MPPH (5.0 mmol), acetonitrile (8 mL). Conditions as described above except no catalyst was used. ^b All quantities are reported as percentages based on amount of cyclohexene used. The errors are estimated to be $\pm(0.03) \times (\% \text{ analysed product})$. ^c Not applicable. ^d Not detected

Scheme 2.1. Potential reactions between cyclohexene and TBHP under free-radical conditions.

2.2.4 Epoxidation of Stilbene:

cis-Stilbene was oxidized using both TBHP and MPPH in order to gain further insight into the oxidative mechanism of the Ti MCM41 catalysts. This olefin can be used to determine whether or not the epoxidation is concerted. Retention of the *cis* conformation will occur if the reaction is concerted. However, a non-concerted, i.e. stepwise, peroxy radical-mediated, process involving a tetrahedral intermediate (of sufficient lifetime), will lead to the thermodynamically more stable *trans* epoxide.

Scheme 2.2. Potential reaction pathways for the oxidation of *cis*-stilbene.

The epoxidation of *cis*-stilbene catalyzed by $\text{Ti}^{\wedge}\text{MCM41}$ using both TBHP and MPPH, (entries 1 and 2 of Table 2.4) demonstrates both the high selectivity of the catalyst and the concerted (non-radical) nature of the reaction. The selectivity for this particular epoxidation would be 100% if it were not for the conversion of some *cis*-stilbene to its *trans* isomer (which occurs because of inadvertent photo-isomerization and acid-catalyzed isomerization on the mildly acidic MCM-41 support). Once again MPPH proved to be a more effective epoxidizing agent than TBHP and, as previously observed, the $\text{Ti}^{\wedge}\text{MCM41}$ is much more reactive than the $\text{Ti}^{\rightarrow}\text{MCM41}$ catalyst.

Table 2.4. *cis*-Stilbene Epoxidation at 25°C in Acetonitrile under Argon ^a

No.	Catalyst	Oxidant	<i>cis</i> -Stilbene Oxide[%]	<i>trans</i> - Stilbene [%]	Selectivity w.r.t. the epoxide [%] ^c	Turnover frequency h ⁻¹ ^d
1	Ti ↑MCM41	TBHP	5.4, 4.1 ^c	1.6, 1.2	77.3, 77.6	3.7, 2.4
2	Ti ↑MCM41	MPPH	16.0, 17.9	0.7, 1.0	95.7, 94.9	9.7, 11.7
4	Ti→MCM41	TBHP	0.3, 0.4	1.8, 2.1	14.2, 17.1	0.1, 0.1
5	Ti→MCM41	MPPH	3.5, 1.9	0.9, 0.4	80.6, 84.5	1.0, 0.5
7	MCM41	TBHP	0.0	3.2	0.0	-
8	MCM41	MPPH	0.0	0.0	0.0	-

^a Amounts given are reported in equivalents of Ti used. ^b The errors are estimated to be $\pm(0.03) \times (\% \text{ stilbene oxide})$. ^cBased on stilbene derived products. ^d Moles of epoxide produced per mole of Ti^{IV} per hour.

The non-radical nature of these Ti (IV)-catalyzed epoxidations becomes very apparent when the results in Table 2.4 are compared to those in Table 2.5. Oxidation of *cis*-stilbene with *tert*-butylperoxyl radicals (generated by the thermal decomposition di-*tert*-butylhyponitrite (BONNOB)) at 37°C in the presence of TBHP, Scheme 2.3, produces benzaldehyde and *trans*-stilbene oxide in approximately equal amounts (together with some *trans*-stilbene, see Table 2.5).

Scheme 2.3. Thermal decomposition of di-*tert*-butyl-hyponitrite to yield alkoxyl radicals and their subsequent reaction to produce peroxyl radicals.

Table 2.5. Reaction of *cis*-Stilbene with Di-*tert*-butyl hyponitrite in the Presence of TBHP ^{a,b}

Experiment	<i>cis</i> -Stilbene oxide	<i>trans</i> -Stilbene	<i>trans</i> -Stilbene oxide	Benzaldehyde
1	0.0	0.18	0.68	0.61
2	0.0	0.19	0.77	0.78

^a Product quantities reported in equivalents of di-*tert*-butyl hyponitrite used. The errors are estimated to be $\pm 3\%$ of the quantity reported. ^b Reaction conditions: di-*tert*-butyl hyponitrite (5.2 mg), TBHP (0.11 ml), and *cis*-stilbene (97.0 mg) were stirred in a solution of glacial acetic acid (0.3 ml) and pyridine (3.0 ml) in a sealed vessel for 72 hours in the dark at 37°C. Products were quantified using an internal standard and a GC equipped with a FID.

These results provide further evidence for the non-radical mechanism of the Ti(IV)-catalyzed epoxidations.

2.3 Discussion

For the first time, it has been demonstrated that the (putative) mechanistic probe, 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH) can be an effective 2-electron oxidant and a suitable replacement for TBHP in 2-electron oxidations. Cyclohexene was selectively and efficiently oxidized in the presence of both hydroperoxides (MPPH, TBHP) and MPPH was not only a better epoxidizing agent than TBHP but also it showed a greater reactivity and selectivity. The reason for the greater reactivity of MPPH becomes obvious following the experiments described in the next section.

2.4 Conclusion

It is clear that MPPH is not “predisposed to radical chemistry” and therefore, MPPH is a suitable replacement for TBHP as a probe for radicals in the oxidation of hydrocarbons mediated by metal catalysts and *tert*-alkyl hydroperoxides.

3 Reactivity of MPPH versus TBHP as Alkene Epoxidation Agents

3.1 Introduction

The results in the previous section showed that MPPH was a better epoxidizing agent than TBHP. One possible reason for this could be a difference in product retardation in the two systems. That is, Sheldon and Van Doorn have reported that the epoxidation of 1-octene by TBHP in benzene at 80 °C on a different $\text{TiO}_2/\text{SiO}_2$ catalyst exhibited marked autoretardation.³⁴ This was attributed to the formation of *tert*-butanol since the reaction rate could also be decreased by the deliberate addition of *tert*-butanol. Although autoretardation was not observed during the epoxidation of cyclohexene under the same conditions, we considered it likely that the enhanced reactivity of MPPH over TBHP on our catalysts was due to differences in the degree of catalyst deactivation by the two alcohols that are co-produced with the epoxide.

To test this hypothesis I decided to study the epoxidation of cyclohexene under the normal conditions described in the previous section with the deliberate addition of alcohols to the acetonitrile solvent. The alcohols used were *tert*-butanol, 1-phenyl-2-methyl-2-propanol, tris-(*tert*-butyl)-carbinol, ethanol, 1-butanol, and 1-decanol. The first two alcohols were chosen because they are products derived from the alkyl hydroperoxides used in the previous study (see Chapter 2). To study steric effects of alcohol inhibition tris-(*tert*-butyl)-carbinol was also used. The alcohols, ethanol, 1-butanol, and 1-decanol were utilized to study hydrophobic / hydrophilic interactions of the alcohols with the catalyst. The steric effects due to these three linear alcohols should be similar.

3.2 Results and Experimental:

Cyclohexene (0.5 mL, 4.9 mmol) was oxidized in the presence of $\text{TiMCM}^{+}41$ (75 mg) and the *tert*-alkyl hydroperoxide (5.0 mmol) in acetonitrile (8 mL). Aliquots of the reaction mixture were removed at timed intervals and quenched with triphenylphosphine. Reaction products were identified and quantified by GC / FID. Four matched experiments with cyclohexene, TBHP and $\text{TiMCM}^{+}41$ were run simultaneously: (i) a normal blank run, (ii) a normal run with added *tert*-butanol (*t*-BuOH) (iii) a normal run with added 2-methyl-1-phenyl-2-propanol (MPPOH), (iv) a normal run with added tris (*tert*-butyl) carbinol (TTBC). The different alcohols inhibited the epoxidation of cyclohexene to different degrees (see Figure 3.1). The addition of *t*-BuOH (11.1 equiv. based on Ti^{IV}) gave the greatest inhibition, the addition of 11.1 equiv. MPPOH retarded the reaction to a much lesser extent, while the addition of TTBC (26.6equiv.) caused very little inhibition. This pattern of retardation was also observed upon the addition of 26.4 equiv. of MPPOH and *t*-BuOH to cyclohexene epoxidations catalyzed by $\text{TiMCM}^{+}41$ with MPPH as the oxidant Figure 3.2 (TTBC was not used in this particular study).

Figure 3.1. Four simultaneously run, matched cyclohexene epoxidations by $\text{Ti}^{\text{IV}}\text{MCM41}$ and TBHP at room temperature under an argon atmosphere: no alcohol added (●), 11.1 equiv. of *t*-BuOH (■), 11.1 equiv. of MPPOH (○), and 26.4 equiv. of TTBC (□). The errors are estimated to be $(0.03) \times (\% \text{ measured cyclohexene oxide})$.

Figure 3.2. Simultaneously run, matched cyclohexene epoxidations by Ti^{MCM41} and MPPH at room temperature under an argon atmosphere in acetonitrile: no added alcohol (●), 26.4 equiv. of t-BuOH (■), 26.4 equiv. of MPPOH (□). The errors are estimated to be $(0.03) \times (\% \text{ measured cyclohexene oxide})$.

It was puzzling that the initial rates of the alcohol inhibited epoxidations were not the same as the rates of the uninhibited reactions at the time when the same amount of alcohol had been produced (i.e., at 11.1 equiv. *t*-BuOH Figure 3.1 and at 26.4 equiv. MPPOH in Figure 3.2). Furthermore, for the MPPH matched experiments the *t*-BuOH showed a much smaller inhibiting effect than it had in the TBHP experiment despite the fact that it was present at twice the concentration (26.4 equiv.) in the MPPH experiment. These results suggested that a significant period of time was required for the alcohol to diffuse into the pores of the catalyst and inhibit the reaction. This seemed reasonable considering the fact the alcohol produced in the epoxidation reaction is made on the interior surface of the catalyst, whereas added alcohol is in the solvent and must diffuse into the MCM-41 support before it can inhibit the reaction.

This time-dependent inhibition was confirmed by stirring the catalyst overnight with 11.3 equivalents of *t*-BuOH. A much stronger inhibition was produced and both the initial rate and the growth curve for epoxide formation (see squares in Figure 3.3) were quite similar to those for the uninhibited reaction from the time at which 11.3 equiv. *t*-BuOH had been produced (see arrow in Figure 3.3 on the curve for no added alcohol).

Figure 3.3. Simultaneously run, matched cyclohexene epoxidations by $\text{Ti}^{\text{IV}}\text{MCM41}$ and TBHP under an atmosphere of argon at room temperature in acetonitrile containing no added alcohol (O), 11.3 equiv. *t*-BuOH added just before the TBHP (●), and 11.3 equiv. *t*-BuOH stirred with the catalyst overnight (□). The errors are estimated to be $(0.03) \times (\% \text{ measured cyclohexene oxide})$.

There were two potential reasons for the observed order of catalyst deactivation by alcohols (*t*-BuOH > MPPOH > TTBC), viz., steric effects and hydrophobic / hydrophilic effects both of which would be expected to have a kinetic component (see e.g., Figure 3.3) and a thermodynamic component. Thus, steric hindrance to the coordination of the alcohol to the Ti^{IV} active site on the $\text{Ti} \uparrow \text{MCM41}$ catalyst surface might be lower for *tert*-butanol than for MPPOH (and TTBC). A consequence of this is that *tert*-butanol would coordinate more strongly to $\text{Ti}(\text{IV})$ than MPPOH and this would impede the coordination of the hydroperoxide to the titanium and hence *t*-BuOH would inhibit epoxidation to a greater extent than MPPOH. Alternatively, the greater hydrophilicity of *t*-BuOH relative to MPPOH (and TTBC) could retard access of the hydroperoxide and / or the cyclohexene to the catalytic surface.

In an attempt to distinguish between these two possibilities, I examined catalyst deactivation by three linear primary alcohols: ethanol, butan-1-ol and decan-1-ol. Their steric effects should be similar, but their hydrophilic character varies substantially. If these three alcohols showed the same degree of inhibition of epoxidation then the different degrees of retardation observed with *t*-BuOH and MPPOH could be attributed to steric effects. But, if the degree of inhibition decreased along the series: ethanol > butan-1-ol > decan-1-ol, then the different degrees of inhibition would have to be attributed either to hydrophobic / hydrophilic effects or to the faster diffusion of the smaller alcohols into the pores of the MCM41.

As can be seen in Figure 3.4 retardation by these alcohols increases from decanol, through butanol, to ethanol. This result is therefore consistent with alcohol-induced $\text{Ti} \uparrow \text{MCM41}$ catalyst deactivation being related either to the hydrophobicity of the alcohol

or to the kinetics of deactivation via alcohol diffusion into the catalyst. In this respect my results are congruent with those obtained by Corma *et al.*³⁵ when they employed a hydrophilic large-pore Ti-beta zeolite and hydrogen peroxide to epoxidize 1-hexene and found that the rate of epoxidation in acetonitrile was twice that in methanol. In contrast, when they employed a hydrophobic, medium-pore titanium silicate catalyst (TS-1) the epoxidation in methanol was three times as fast as that in acetonitrile.

Our results have two implications for any practical applications of Ti^{IV}MCM41 as an olefin epoxidation catalyst. First, MPPH gives a higher yield of cyclohexene oxide than TBHP because of the differences in the hydrophobicities and/or the diffusivities of the corresponding alcohols formed during the reaction, and *not* (apparently) because of any differences in the reactivities of the two *tert*-alkyl-hydroperoxides. Therefore, with this particular catalyst, more efficient epoxidations will be achieved using large hydrophobic rather than small hydrophilic alkyl hydroperoxides. Second, the choice of solvent will be critical, with alcohols being the very worst solvents to employ (see Table 3.1). In this connection, it is interesting to note that Corma *et al.*³⁵ and of Clerici and Ingallina³⁶ have reported that for epoxidations using the TS-1 catalyst methanol was the best solvent with activity decreasing in the order: MeOH > EtOH > t-BuOH.

Figure 3.4. Simultaneously run, matched cyclohexene epoxidation by Ti^{IV}/MCM 41 and TBHP containing 11.2 equiv. of ethan-1-ol (O), 11.2 equiv. of butan-1-ol (□) or 11.2 equiv. of decan-1-ol (●). The errors are estimated to be $(0.03) \times (\% \text{ measured cyclohexene oxide})$.

Table 3.1: The effect of Solvent on Cyclohexene Epoxidation by Ti^{IV} MCM41 and TBHP under an atmosphere of argon at room temperature.^a

<i>Solvent</i>	<i>Cyclohexene oxide (Ti^{IV} equiv.)</i>		
	4h ^b	8h ^b	24h ^b
Acetonitrile	7.4	16	21
Isooctane	6.7	11	14
Pyridine	0.0002	0.52	1.8
Methanol	0.00	0.094	0.44
2-propanol	0.004	0.17	0.28

^a Simultaneously run, matched cyclohexene epoxidations by Ti^{IV} MCM41 and TBHP under an atmosphere of argon at room temperature. Experimental conditions described in section 2.2.1. ^b The reaction time at which samples were analyzed. The errors are estimated to be $(0.03) \times (\% \text{ measured cyclohexene oxide})$.

The ideal solvent for the olefin epoxidation using the Ti^{IV} MCM41 catalyst and *tert*-alkyl hydroperoxides is one which is not a hydrogen bond donor (HBD) and is also only a relatively poor hydrogen bond acceptor (HBA). If the solvent is a strong HBA it would be expected to deactivate the catalyst (via any surface hydroxyl groups) and also deactivate the hydroperoxide (via $\text{ROOH} \cdots \text{HBA}$ hydrogen bonding). These deductions are supported by the fact that epoxidation was very inefficient in the very good HBA solvent, pyridine (and this was not because the oxidation was “diverted” since pyridine-N-oxide was not detected after 24 h). On the other hand, if the solvent is not a HBA it will only poorly solvate the alcohol formed from the hydroperoxide in the epoxidation process and will therefore tend to “leave” the alcohol in the hydrophilic pores of the catalyst where it will inhibit the reaction. In support of this deduction, we note that the yield of cyclohexene oxide was lower in isooctane than acetonitrile. A nice balance

between these various solvent requirements is achieved for $\text{Ti}^{\text{IV}}\text{MCM41}$ by using acetonitrile which may be well be the optimum solvent for these epoxidation reactions.

The results on the solvent effect are shown in Table 3.1. From the solvent effects on the rate of epoxide formation it can be seen that the reaction is fastest in acetonitrile and that it hardly occurs in pyridine, methanol and *iso*-propanol. These results imply that the solvent plays an important role solvating the *t*-BuOH generated from the TBHP.

4 Kinetics of Radical Reactions

4.1 Introduction:

The aims of chemical kinetics are: (1) to experimentally determine the rate of a reaction and its dependence on parameters such as concentration, temperature, and catalysts; and (2) to understand the mechanism of a reaction, that is, the number of steps involved and the nature of any intermediates which may be formed.

4.1.1 The Rate Equation

The interpretation of kinetic data begins with a hypothetical sequence of elementary reaction steps, each characterized by two microscopic rate constants, one for the forward and one for the reverse reaction. From this hypothetical mechanism a rate equation is derived, predicting the dependence of the observed reaction rate on concentrations and on microscopic rate constants, and its form is tested against experimental observations. If the form of the rate equation meets the test of experiment, it may be possible to derive from the data numerical values for the microscopic rate constants of the proposed elementary reaction steps. While inconsistency is clear grounds for modifying or rejecting a mechanistic hypothesis, agreement does not prove the proposed mechanism correct.

4.1.2 Rates of Reactions

Consider a reaction of the form $aA + bB \longrightarrow cC$, the concentrations of the species being $[A]$, $[B]$, and $[C]$ at some instant in time. The change of concentration of a specified component with respect to time, denoted by v_J i.e., the rate of change of species J , for the present example is given by

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Equations 4.5 and 4.6 constitute a mathematical model for the dynamics of equation 4.4, and the predicted rates of change of the constituent concentrations are given by sums of terms, each of which contains only the first power of one of the concentrations. Therefore, the kinetics are said to be first order. In the reaction given in equation 4.4 we have assumed the reaction is: A changes to B and B changes to A without the intervention of a third species, say I; that is, A changes to I and I changes to B.

The reaction in equation 4.4 is an elementary step, because it has been implied that there are no intermediates

A first order unimolecular reaction may be simplified in many cases because $k_1 \gg k_{-1}$. Then the chemical equation can be written as follows:

And the rate law for the disappearance of reactant A is given by

$$-\frac{d[A]}{dt} = k_1[A] \quad 4.9$$

The differential equation is easily solved, the boundaries are: at $t=0$ the concentration of A is $[A]_0$, and at time t it is $[A]_t$, hence

$$[A]_t = [A]_0 e^{-k_1 t} \quad 4.10$$

A similar expression is obtained in terms of B, except that the solution will be an exponential growth.

4.1.4 Second Order Reactions

Second-order kinetics arise when sum of the powers of the of the reagent concentrations in the rate law is equal to two. Two cases will be presented.

Case 1) An elementary reaction in which the encounter of A with A may form an *activated complex* and give product C

The rate law is given by:

$$-\frac{d[A]}{dt} = k_{11}[A]^2 \quad 4.12$$

The solution to equation 4.12 is given by :

$$A_t = \frac{[A]_0}{1 + kt_{11}[A]_0} \quad 4.13$$

If a reaction is second-order a plot of $1/[A]_t$ against t is expected to yield a straight line, and the slope of the line is equal to the rate constant; i.e.,

$$\frac{1}{A_t} = \frac{1}{A_0} + k_{11}t \quad 4.14$$

Case II)

An elementary reaction in which the encounter of two reactants, A and B, may form an *activated complex* and in turn may be transformed into product C, that is

The rate law for this “mixed-second-order” kinetics,

$$-\frac{d[A]}{dt} = k[A][B] \quad 4.16$$

is one of the most widely encountered kinetic forms in chemistry. By making the appropriate substitutions, $-d[A]/dt = \{[A]_0 - x\}/dt = dx / dt$

$$kt = \frac{1}{[A]_0 - [B]_0} \ln \left\{ \frac{[A]_t [B]_0}{[A]_0 [B]_t} \right\} \quad 4.17$$

4.1.5 The Pseudo First Order Reaction

Equation 4.17 can be greatly simplified if the concentration of one reagent is kept constant during the reaction. The easiest way of achieving this is to have one reagent in a large excess relative to the other such that the rate of change of its concentration over time is essentially zero. In the bimolecular reaction, equation 4.15, if B is put at a large excess over A and is considered to remain constant over the course of the reaction we can write:

$$-\frac{d[A]}{dt} = k_{obs}[A] \quad 4.18$$

where

$$k_{obs} = k[B] \quad 4.19$$

The absolute bimolecular rate constant is obtained by measuring the rate in the presence of a large excess of B over A, then dividing the observed rate by the concentration of B. To reduce experimental-errors, it is best to measure the rate of the reaction (k_{obs}) with at

least five different concentrations of B (all in a large excess relative to A) and then plot k_{obs} against the concentration of B. The slope of this plot furnishes the absolute bimolecular rate constant.

4.1.6 Half Lives

A useful indication of the rate of chemical reaction is the time it takes for the concentration of a substance to fall to half of its initial value. The half-life depends on the initial concentration of the substance in a characteristic way that depends on the order of the reaction, and so its measurement is a guide to the reaction order.

The equation for half lives are obtained by solving equation 4.9 for the case when the concentration of [A] decreases from $[A]_0$ to $\frac{1}{2}[A]_0$.

For a first order reaction, the half life is given by

$$t_{1/2} = \frac{\ln 2}{k} \quad 4.20$$

Note, for a first order reaction the half life is independent of the initial concentration, A_0 .

In the case of a second order reaction (in A; i.e. equation 4.11) the equation for the half-life is easily obtained by making the appropriate substitutions in the rate law for a second order reaction.

$$t_{1/2} = \frac{1}{k[A]_0} \quad 4.21$$

4.2 Techniques for Measuring Radical Kinetics.

The best techniques either detect the radical and permit its concentration (or relative concentration) to be monitored during the course of the reaction, or detect some

other non-radical reactant or product and permit its concentration (or relative concentration) to be monitored. Direct monitoring of an elementary reaction requires time resolved methods which should be available over a wide range of time scales. Bimolecular reactions may require time scales which can range from nanoseconds to seconds, or even minutes or hours, while for *ultrafast* unimolecular reactions, and in cage processes, a time scale of picoseconds may be required. The methods allowing time resolved monitoring of elementary reactions are referred to as direct methods.

To overcome the need for expensive and sometimes elaborate instrumentation several indirect methods have been developed which are based on reaction product analyses.

A general survey of kinetic techniques will be given which focuses on techniques relevant to the present work.

4.2.1 Flash Photolysis

Flash photolysis is a valuable method for the generation of radicals by a short, sharp pulse of light. This method allows the essentially “*instantaneous*” generation of a relatively high concentration of radicals. Because most radicals are fairly reactive, (at least in radical-radical reactions if not always in radical-molecule reactions) they have short lifetimes. Therefore, the main problem is not just to generate the radical, but also to detect and identify it, then determine its rate of reaction with a chosen substrate, all on a very short time scale.

The basic flash photolysis apparatus consists of the photochemical irradiation unit, a sample unit and a detection system for transient species. The detection system is

usually a fast response spectroscopic detector such as an UV spectrometer, a fluorimeter or an IR spectrophotometer which permit determination of the absorption (or emission) spectrum of the transient during the reaction. The detector is usually set to monitor a single wavelength as a function of time. The chosen wavelength is one at which the transient species shows a characteristic absorption, ideally a wavelength that is exclusive to that species. The actual monitoring wavelength is chosen after examining as complete a spectrum of the transient as possible.

The equipment has an electronic control, which triggers the flash of light that is focussed onto the sample and generates the transient radical from a suitable precursor. The wavelength used for the photoflash depends on the flash unit used and the absorption spectrum of the reagent. After radicals are generated they will decay by reaction with the substrate which has been added at a known concentration to the sample. After flash-photolysis, a UV-Vis lamp (or IR source) is triggered and the absorption of the transient species is recorded as a function of time as light passes through the sample and into the detector. A monochromator is positioned between the detector and the sample. The signal from the photomultiplier tube is displayed on an oscilloscope screen and is digitized for computer treatment.

4.2.1.1 Laser flash photolysis (LFP)

The component parts used for a typical laser flash photolysis experiment are shown in Figure 4.1. They include: the sample cell, monitoring source (lamp), excitation source (the laser), optical lenses and filters, detector, analysis/output devices (digitizer/computer).³⁷

Figure 4.1. Schematic diagram of laser flash photolysis apparatus with UV-Vis detector.

Sample Cell

The samples cells used were 7 x 7 mm Suprasil quartz tubes.

Monitoring source

The lamp used for monitoring was a xenon arc lamp with an out put of ~ 75 W. The transients monitored for this thesis have small extinction coefficients so the monitoring lamp is operated in a pulse mode; i.e., the intensity is increased by a factor of 20-100 during the essential few milliseconds. The monitoring beam was focused to a ~1 mm radius where it passes through the sample.

Laser Excitation Source

One of the most important aspects of any LFP experiment is the selection of the appropriate laser.

- Wavelength

The laser used in the experiments described in this thesis was a Lumonics Excimer 500. A gas mixture of 40 Torr xenon, 50 Torr of a gas mixture made of 5% HCl, 1% H₂ and 94% neon, and 60 psi of neon provide an excitation wavelength of 308 nm.

- Energy per Pulse

The output of the laser was generally 35-70 mJ. Neutral density filters were used to attenuate the output in order to avoid high concentrations of transients which would decay with second-order kinetics.

- Pulse duration

The pulse duration, or pulse width of the laser was approximately 6 ns.

Detector

The detector for the laser flash experiments consisted of a monochromator / photomultiplier tube (MC/PMT) combination. The PMT is located behind the MC. The

photons strike the cathode of the PMT and an electron is emitted. The PMT is wired to a six-dynode chain for fast response and to prevent saturation at high light intensities.

Gathering Data

Transient digitizers are used to convert the PMT out-put into digital form and transfer this data to a computer for further processing. The digitizer used was a Tektronix, model 7912AD programmable digitizer.

Data Processing

The data produced by the laser flash is the intensity of the monitoring beam and an array of data points, exactly 100, in the form of PMT voltage as function of time. The data points are converted into changes in optical densities via the equation below.

$$A_t = \Delta OD = -\log(1 - \text{signal} / IO) = -\log(I_t / IO) \quad (4.22)$$

where IO is the intensity of the monitoring beam measured as a voltage, and signal is the signal voltage as a function of time. I_t is equal to $IO - \text{signal}$. The signal created was captured by a Tektronix 2440 digital storage oscilloscope which was interfaced to a 386 SX personal computer. The program used to analyze the data was written in FORTRAN.

Corrections to the Data

To improve the quality of data two different types of corrections may be required, namely 'baseline' and 'fluorescence' corrections.

Baseline Correction

Noise due to the electronics of the laser and the lamp in addition to baseline drift, may be reduced by baseline correction. The baseline correction is achieved by subtracting a signal containing only the monitoring beam (laser blocked) from one containing the

transient (laser on) on top of the monitoring beam. This method was used for time domains up to a microsecond.

Fluorescence Correction

Species in the sample that fluoresce will contribute to decreases in the apparent adsorption. To correct for this the signal is recorded with the monitoring beam on and off while the laser is firing. This correction must also be made when the time domain is approaching the laser pulse width.

Samples

Samples were prepared at a concentration such that the OD at 308 nm was ~0.3 in the 7 x 7 mm Supracil quartz cell. Samples were flashed no more than 10 times and fresh samples were prepared for each kinetic measurement.

4.3 Competitive Kinetics

The method of laser flash photolysis was utilized for studying the reactions of an alkoxyl radical with most of the phenols I employed. However, this was not possible for all phenols. Complications that may arise when utilizing LFP for measuring rate constants include:

- i) the phenol may absorb at the excitation wavelength of the laser
- ii) the solvent may absorb at the excitation wavelength

To overcome these problems the “old fashioned” method of competitive kinetics was employed. Competitive kinetics provides relative rates. That is, it is not a method which directly gives absolute rate constants, rather it measures the rate of a reaction relative to another reaction.

Competition methods involve *post facto* analysis of product mixtures, in this case by gas chromatography with flame ionization detection. Competition kinetic methods require partitioning of a radical intermediate between two reaction channels, the reaction of interest with an unknown rate constant and the basis reaction with a known rate constant. In principal, any competing reactions can be employed, but in practice, one usually prefers a situation where one reaction is unimolecular and the other is bimolecular. The cumyloxyl radical is very suitable for competitive kinetics since the rate constants for hydrogen atom abstraction from hydrogen atom donors, which yields cumyl alcohol can be made competitive with its unimolecular β -scission, which yields acetophenone. A convenient and clean source of cumyloxyl radicals is dicumyl hyponitrite which undergoes a facile thermal decomposition at ambient and higher temperatures.

Figure 4.2. The generation of cumyloxyl radicals by the thermal decomposition of dicumyl hyponitrite and two possible reaction pathways for the resulting alkoxyl radical.

The scheme shown in Figure 4.2 is an ideal case; i.e., there is only one competing process. However when using competitive kinetics all of the possible reaction pathways

must be considered. The cumyloxyl radical might, in some cases, also abstract a hydrogen atom from the solvent (SH), and from the dicumyl hyponitrite (P).

First, consider the rate of formation of the alcohol, reactions 4.25-4.27.

$$\frac{d[\text{ROH}]}{dt} = k_{\text{XOH}}[\text{RO}\bullet][\text{XOH}] + k_{\text{SH}}[\text{RO}\bullet][\text{SH}] + k_p[\text{RO}\bullet][\text{RONNOR}] \quad 4.28$$

R represents the cumyl group, thus RO• represents the cumyloxyl radical. XOH is a hydrogen atom donor under investigation, for example a substituted phenol and the solvent is SH, and RONNOR represents the dicumyl hyponitrite. The rate constants are denoted by k and the subscript is the hydrogen donating species. Equation 4.28 can be simplified by invoking pseudo-first-order-reaction conditions, the solvent SH will always be in great excess, and we ensure that the hydrogen atom donor XOH is also in large excess such that its concentration changes very little over time, thus equation 4.28 becomes

$$\frac{d[\text{ROH}]}{dt} = k'_{\text{XOH}} [\text{RO}\bullet] + k'_{\text{SH}} [\text{RO}\bullet] + k_p[\text{RO}\bullet][\text{RONNOR}] \quad 4.29$$

where $k'_{\text{XOH}} = k_{\text{XOH}} [\text{XOH}]$ and $k'_{\text{SH}} = k_{\text{SH}} [\text{SH}]$

The rate of hydrogen atom abstraction from the RONNOR is expected to be slow with respect to other three reaction channels described in equation 3.29, i.e.,

$$k'_{\text{XOH}}[\text{RO}\bullet] \gg k_p[\text{RONNOR}] \quad \text{and} \quad k'_{\text{SH}}[\text{SH}] \gg k_p[\text{RONNOR}]$$

thus equation 4.29 becomes;

$$\frac{d[ROH]}{dt} = k'_{XOH} [RO\bullet] + k'_{SH} [RO\bullet] \quad 4.30$$

Now consider the remaining reaction channel, our basis reaction, the β -scission of the cumyloxyl yielding acetophenone [PhCOMe]. The rate law is,

$$\frac{d[PhCOMe]}{dt} = k_{\beta} [RO\bullet] \quad 4.31$$

Dividing equation 4.30 by equation 4.31 yields

$$\frac{\frac{d[ROH]}{dt}}{\frac{d[PhCOMe]}{dt}} = \frac{k'_{XOH} [RO\bullet] + k'_{SH} [RO\bullet]}{k_{\beta} [RO\bullet]} \quad 4.32$$

canceling the like terms in equation 4.32 we arrive at an expression that is independent of the cumyloxyl radical concentration, and the variable time, t , has been eliminated

$$\frac{d[ROH]}{d[PhCOMe]} = \frac{k'_{XOH} + k'_{SH}}{k_{\beta}} \quad 4.33$$

Integration between the limits

$[ROH] = 0$ to $[ROH] = [ROH]$ and $[PhCOMe] = 0$ to $[PhCOMe] = [PhCOMe]$

$$\frac{[ROH]}{[PhCOMe]} = \frac{k'_{XOH} + k'_{SH}}{k_{\beta}} \quad 4.34$$

replacing the pseudo first order rate constants yields

$$\frac{[ROH]}{[PhCOMe]} = \frac{k_{XOH}}{k_{\beta}} [XOH] + \frac{k_{SH} [SH]}{k_{\beta}} \quad 4.35$$

To use equation 4.35 we measure the concentrations of the cumyl alcohol (ROH) and acetophenone (PhCOMe) upon completion of the reaction, i.e. when > 99% of the dicumyl hyponitrite has decomposed. The relative rate constants k_H / k_{β} can be obtained

from the slope of a graph of $[\text{ROH}] / [\text{PhCOMe}]$ versus $[\text{XOH}]$. The absolute rate constant k_{H} is obtained by multiplying the slope of the graph by the rate constant for β -scission, k_{β} .

There are some limitations to this procedure. One limitation is the choice of solvent, although this is a factor in laser flash experiments as well. The competitive kinetics technique is limited to solvents that are not hydrogen atom donors or are only poor donors at best. The reason for this stems from equation 4.35. There is a solvent dependent term; thus, if the solvent is a good hydrogen atom donor then all of the alkoxy radicals will abstract a hydrogen atom from SH and hence the relative concentrations of cumyl alcohol and acetophenone will not depend upon the concentration of XOH.

5 Linear Free Energy Relationships (LFER)

5.1 Introduction

It has been customary for chemists accumulating data on reaction rates and equilibria to formulate empirical correlations. The most common relationship is a linear correlation between the logarithms of rate or equilibrium constants for one reaction series and the logarithms of rate or equilibrium constants of a second reaction series, both sets being subjected to the same variation, either structural, or environmental. To illustrate consider the situation when the logarithm of the rate constants for a reaction series can be linearly correlated with the logarithm of the equilibrium constants of another reaction series, that is

$$\log \frac{k_A^i}{k_A^j} = m \log \frac{K_B^i}{K_B^j} \quad 5.1$$

OR

$$\log k_A = m \log K_B + b \quad 5.2$$

The logarithmic terms are linearly related to free energy changes:

$$\log k_A^i = -\frac{\Delta G_A^\ddagger}{2.3RT} + \log \frac{kT}{h} \quad 5.3$$

$$\log K_B^i = \frac{-\Delta G_B^\circ}{2.3RT} \quad 5.4$$

Combining equation 5.2-5.4

$$\Delta G_A^\ddagger = m \Delta G_B^\circ + b \quad 5.5$$

Such a correlation is called *linear free energy relationship* (LFER).

5.1.1 The Hammett Equation and σ Constants

A problem that has challenged chemists for years is the determination of the electronic influence that a substituent exerts on the rate and course of a reaction.

Hammett^{38,39} recognized that the electronic influence of a substituent X could be assessed by studying an equilibrium constant or a rate of a reaction involving a side chain, Y, in a meta- or para- di-substituted benzene.

He deliberately did not deal with ortho substituents because they clearly could have both electronic *and* steric effects on Y.

The standard reaction series chosen by Hammett was the dissociation constant of 3- and 4-X-benzoic acids in water at 25 °C.

Consider the free energy change ΔG_0° in dissociation of benzoic acid (X = H) and the free energy of dissociation of a substituted benzoic acid, ΔG° . The latter can be regarded as ΔG_0° plus an increment, $\Delta\Delta G^\circ$, contributed by the substituent, X.

$$\Delta G^\circ = \Delta G_0^\circ + \Delta\Delta G^\circ \quad 5.6$$

Since $\Delta G = -2.303RT \log(K_{eq})$ and a parameter, σ , can be defined for each substituent X so that it causes a change in the free energy by

$$\Delta\Delta G^\circ = -2.303RT\sigma \quad 5.7$$

$$\Delta G^\circ = \Delta G_o^\circ - 2.303RT\sigma \quad 5.8$$

The appropriate substitutions can be made for the free energy

$$2.303RT \log K = 2.303RT \log K_o + 2.303RT\sigma \quad 5.9$$

This can be rearranged into the Hammett equation

$$\log \frac{K}{K_o} = pK_o - pK = \sigma \quad 5.10$$

This equation defines meta and para substituent constants, σ_m and, σ_p that are based on the dissociation of benzoic acid in water at 25°C. A plot of $\log K$ vs. σ will have a slope of one as defined by equation 5.10. In order that equation 5.10 may be applied to other equilibria or reactions it is modified to equation 5.11,

$$\log \frac{K}{K_o} = pK_o - pK = \rho\sigma \quad 5.11$$

where ρ is the slope of the LFER and is called the reaction constant. Several σ constants are given in Table 5.1.

Although the Hammett σ substituent constants were found adequate to relate the rate and equilibrium constants for a large number of reactions, they were sometimes unsuccessful. Other types of σ constants have therefore been defined, of most importance are σ^+ and σ^- .

5.1.2 Brown and Okamoto's σ^+ Substituent Constants

The σ constants developed by Hammett provided an exceedingly valuable means for correlating the effects of substituents on the rates and equilibria for a massive number of processes involving substituted benzenes. The Hammett equation proved to be particularly successful when the substituents exerted their effect chiefly through inductive or electrostatic forces; however, when resonance interactions between X and Y were possible Hammett's σ constants correlated the data rather poorly. To overcome many of these problems Brown and Okamoto⁴⁰⁻⁴² developed a new substituent constant, σ^+ , that relates the interaction between an electron-deficient reaction site and a substituent when through resonance is possible.

Table 5.1. σ , σ^+ , and σ^- values for some common aromatic substituents.

Substituent	σ_p	σ_m	σ_p^+	σ_p^-
NMe ₂	-0.83	-0.16	-1.70	-0.12
NH ₂	-0.66	-0.16	-1.30	-0.15
OH	-0.37	0.12	-0.92	-0.37
OMe	-0.27	0.12	-0.78	-0.26
CMe ₃	-0.20	-0.10	-0.26	-0.13
Me	-0.17	-0.07	-0.31	-0.17
H	0	0	0	0
Ph	-0.01	0.06	-0.18	0.02
F	0.06	0.34	0.57	-0.03
Cl	0.23	0.37	0.11	0.19
Br	0.39	0.23	0.15	0.25
COMe	0.50	0.38	0.87	0.84
CF ₃	0.43	0.54	0.61	0.65
CN	0.66	0.56	0.66	1.00

^a All Values obtained from the literature.^{39,43}

$$\log \left(\frac{k}{k^0} \right) = \rho^+ \sigma^+ \quad (5.12)$$

The standard reaction for the evaluation of σ^+ parameters is based on the relative rates of solvolysis of meta- and para-substituted cumyl chlorides in 90% aqueous acetone at 25°C.

Table 5.1 lists some σ^+ constants.

Some rates and equilibria data for substituted benzenes could not be correlated with either σ or σ^+ constants. These were for processes in which the reaction site became electron rich (rather than electron poor for which σ^+ provided the correlations).

5.1.3 The σ^- Constant

The σ^- parameter was developed for situations in which meta and para substituents, X, on the aromatic ring interact with a reaction site that becomes electron rich and when through resonance is possible. The standard reactions for the evaluation of σ^- is the ionization of substituted phenols and anilinium ions in water and / or methanol at 25°C.³⁸

5.13

Some σ^- constants are also listed in Table 5.1.

5.1.4 The Reaction Constant ρ

Usually the most convenient way to use the Hammett equation is to plot $\log K/K_0$ (or $\log k$) or $\log k/k_0$ (or $\log k$) on the vertical axis and the substituent constant on the horizontal axis. A reasonable fit to a straight line indicates that a LFER has been found, and the substituent constant can be used to describe the reaction of interest, to help understand electron flow as the reactant is converted to product (i.e., to understand the reaction mechanism) and to predict results for other substituents which were not studied but for which the appropriate σ values are available. If a LFER is found using σ constants then the slope is denoted as ρ , if a LFER is found utilizing σ^+ or σ^- then the slope is denoted by ρ^+ or ρ^- , respectively.

Simply put, the magnitude of ρ measures the susceptibility of a reaction to the influence of substituents. If ρ is positive it means that the reaction responds to substituents in the same sense as does the standard reaction that defines the substituent constants and for which $\rho = 1.0$ in all these cases. A negative ρ value means that the reaction of interest responds in the opposite manner with respect to the reaction defining the substituent constants.

It is important to recognize that the ρ -value depends on the reaction series and is independent of the substituents actually employed to determine ρ . Thus, when a LFER is found in the form of the Hammett equation a comparison is possible between the standard reaction series (i.e., dissociation of 3- and 4-substituted benzoic acids) and the reaction of interest.

For the reaction series discussed above that defined σ , σ^+ and σ^- , the reactants comprise a number of functionally related compounds, e.g. 3- and 4-X-phenols. There are, however, a multitude of reaction series in which the reactants are fixed, but the solvent is varied.

5.2 Solvent Parameters

5.2.1 Introduction

The Hammett and Hammett type parameters just described, can be used to create LFER for a series of structurally related compounds in the same reaction medium. LFER may also be constructed for one compound or reaction in a number of different media; i.e., solvents. The parameters required to fit a LFER will describe some property of the solvents.

One of the most important characteristics of a solvent is its polarity. The polarity of a solvent may be described by several parameters. Those which are most frequently employed are the dielectric constants (ϵ), dipole moment (μ), Winstein-Grunwald Y value, Kosower Z value, Dimroth and Reichardt $E_T(30)$, and Knauer –Napier A_N values. The dielectric constant and dipole moment differ from the other four solvent parameters in two important ways.

First ϵ and μ do not probe the arrangement and effect of those solvent molecules which are in the cybotactic region i.e., the region in the immediate vicinity of the solute. The dielectric constant of the solvent does not probe the cybotactic region because it is a macroscopic property of the bulk solvent. The dipole moment of the solvent does not probe the cybotactic region because it is a property of an individual solvent molecule. In contrast, Y , Z , $E_T(30)$, and A_N values derive from experiments which do probe the cybotactic region.

The second important way in which ϵ and μ differ from Y , Z , $E_T(30)$, and A_N is that the latter four can be regarded as model dependent measures of solvent polarity since they are based on a particular effect on a particular chemical process. In contrast, ϵ and μ

can be regarded as non-model-dependent parameters of solvent polarity since no model reaction is involved in their determination.

If a solvent polarity parameter is to be used to correlate the effects of solvents on, e.g., reaction rate, then it is essential that the parameter reflects the properties of the cybotactic region, because reaction rates are molecular properties and will be more strongly influenced by local effects of the solvent in the cybotactic region than any properties of the bulk solvent.

5.2.2 Solvent Effects on UV-Vis Adsorption

Solvent effects on organic reactivity and on absorption spectra have generally been rationalized in terms of “solvent polarity”. Solvent polarity is used to relate the capacity of a solvent to solvate dissolved charged, or dipolar, species. This concept of solvent polarity is easily grasped qualitatively, but it is difficult to define precisely and express quantitatively. Attempts to express it quantitatively have often involved physical properties of bulk solvent such as dielectric constant or refractive index, or of the individual solvent molecule such as its dipole moment. These approaches are usually inadequate since the solvents are treated essentially as a non-structured continuum, rather than being composed of individual solvent molecules with various solvent-solvent interactions, and specific solvent-solute interactions.⁴⁴

The band maximum, intensity and shape of the UV-Vis adsorption spectrum of a solute in a series of solvents are frequently solvent dependent. These changes are a result of physical, intermolecular solute-solvent interaction forces (such as ion-dipole, dipole-dipole, dipole-induced dipole, hydrogen bonding, etc.). These interactions cause a change

in the energy required for electronic excitation and hence in the position of the band maximum and its intensity. This is referred to as solvatochromism.

A qualitative interpretation of solvent induced shifts in a band maximum is possible by considering: 1) the momentary transition dipole moment present during the optical absorption, 2) the difference in permanent dipole moment between the ground and excited state of the solute, 3) the change in the ground-state dipole moment of the solute induced by the solvent, 4) the Frank-Condon principle.

Figure 5.1. Schematic qualitative representation of solvent effects on the electronic transition energy of dipolar solutes in polar solvents.

The observed shift of a chromophore's band maximum upon changing the solvent from non-polar to polar will depend upon the stabilization effect the solvent has on both the ground state and excited state. For polar solutes the two possible situations are described in Figure 5.1. If stabilization of the ground state is small compared to the excited state, Figure 5.1a, an increase in solvent polarity will produce a bathochromic (red) shift in the absorption band maximum. Conversely, if the ground state stabilization

is large compared to the excited state, Figure 5.1b, then a hypsochromic (blue) shift of the band maximum will occur as the solvents become more polar.

5.2.3 Dimroth-Reichardt $E_T(30)$

Dimroth and Reichardt have proposed a standard reaction series based on the transition energy for the longest-wavelength solvatochromatic absorption band of the pyridinium-N-phenoxide betaine, denoted by $E_T(30)$,^{44,45} to characterize solvent polarity in the cybotactic region, i.e., $E_T(30)$ is a solvent parameter.

The $E_T(30)$ parameter, expressed in kcal/mol is determined from the absorption band via equation 13

$$E_T(30) / (\text{kcal} \cdot \text{mol}^{-1}) = h \cdot c \cdot \tilde{\nu} \cdot N_A \quad 5.13$$

where h is Planck's constant, c is the velocity of light in a vacuum, $\tilde{\nu}$ is the wave number of the photon which produces the electronic excitation, and N_A is Avogadro's number.

Examples of $E_T(30)$ values for a few solvents are given in Table 5.2.

5.2.4 Knauer-Napier a^N Solvent Parameter

Another parameter that probes the cybotactic region is Knauer and Napier's A_N values.⁴⁶ The A_N parameter reflects the particular effect solvents have on the ^{14}N isotropic hyperfine splitting constant of a stable nitroxide radical. The electron spin resonance (ESR) spectra of nitroxides are sensitive to the polarity of the solvent in which they are dissolved. In terms of valence bond theory two canonical structures (Ia and Ib) can be drawn for the nitroxide radical.

The greater the polarity of the solvent, the more is structure Ib favored with an increase in the electron density on oxygen and an increase in the spin density on nitrogen and consequently, an increase in A_N .

Knauer and Napier defined a solvent parameter that is derived from the ^{14}N hyperfine splittings in the ESR spectra of di-*tert*-butyl nitroxide, 4-amino-2,2,6,6-tetra.methylpiperid-1-yloxy, and 3-carbamoyl-2,2,5,5,-tetramethyl-3-pyrrolin-1-yloxy. The effects of solvents on the A_N values for these three nitroxides are so similar that normally only the A_N values for 4-amino-2,2,6,6-tetramethylpiperin-N-oxyl are utilized.²¹

Table 5.2. Solvent polarity as described by the $E_T(30)$ and A_N solvent parameters.

Solvent	$E_T(30)^a$	A_N^b
tetrachloromethane	32.4	15.404
benzene	34.3	15.532
diethyl ether	34.5	15.421
chlorobenzene	36.8	15.563
pyridine	35.5	15.663
DMSO	45.1	15.771
acetonitrile	45.6	15.761
acetic acid	51.7	16.189
methanol	55.4	16.199

^a Values gathered from the literature. ⁴⁴ ^b Values gathered from the literature. ⁴⁶

6 Hydrogen Bonding

6.1 Introduction

Hydrogen bonds are the most important ‘weak’ interactions encountered in solid, liquid and gas phases. They define the crystal packing of many organic compounds and the 3D structure of biological macromolecules such as DNA.^{47,48} They also modulate the reactivity of different groups within a molecule. It is arguable that the hydrogen-bond is one of the most important interactions in nature.

Hydrogen-bonds (HBs) can be either intra- or inter-molecular. They can be defined as an attractive interaction between two molecular moieties in which a hydrogen atom plays a fundamental role.⁴⁹

The classical HBs correspond to those formed between two heteroatoms, A and B, with a hydrogen atom bonded to one of these atoms and located approximately on the straight line defining the least distance between A and B ($A-H\cdots B$). There is generally, an electrostatic attraction between the positive end of the A-H dipole ($\delta^-A-H\delta^+$) and the center of high electron density located on B (generally a lone pair of electrons). Usually, the A-H moiety is defined either as an ‘electron-pair acceptor, EPA’ or a ‘hydrogen bond donor HBD’ and the B moiety as an ‘electron pair donor, EPD’ or a ‘hydrogen bond acceptor HBA’. In the text to follow, HBA and HBD will be used throughout.

In the rank of interactions among atoms, the HB falls between formal and strong chemical bonds (e.g. covalent bonds) and weak, formally non-bonding interactions, e.g., van der Waals’ interactions. Three different types of hydrogen bonds have been defined. These definitions depend upon the interaction energy, or enthalpy; weak HBs have

energies between 1-4 kcal mol⁻¹, moderate HBs have energies ranging from 5-14 kcal mol⁻¹, while strong HBs have energies extending from 15-40 kcal mol⁻¹.⁴⁷

6.1.1 Maria-Gal Basicity Parameter θ

The ubiquitous nature of the HB has prompted a great effort to characterize hydrogen-bonding by empirical parameters. Maria and Gal have attempted to rationalize this area through a principle-component analysis of different basicity scales, or basicity dependent properties (BDP).⁵⁰ They identified two main components, F_1 and F_2 , which can be used to designate BDPs through equation 6.1:

$$BDP = BDP_o + S_1 F_1 + S_2 F_2 \quad 6.1$$

BDP represents some basicity-dependent property of a series of compounds; for example, log K for proton acceptor equilibria in water, or the standard molar enthalpy of 1:1 adduct formation of an H-bond accepting solvent with gaseous boron-trifluoride,⁵¹ $\Delta H_{D-BF_3}^0$, in dilute dichloromethane solution at 298K, according to equation 6.2.

BDP_o and S_1 and S_2 (equation 6.1) are constants determined through linear regression analysis. The term F_1 “appears as a blend of electrostatic (ES) and electronic-delocalization or charge transfer (CT) contributions to the acid base interaction”. The term F_2 is “electrostatic in nature and may have polarization associated with it”. Maria and Gal have transformed equation 6.1 into polar coordinates, the corresponding vector has a modulus of $\rho = (S_1^2 + S_2^2)^{1/2}$ and is at an angle $\theta = \arctan(S_2/S_1)$. The angle θ , experimentally obtainable, is characteristic of the electrostatic: covalent ratio in complexes between a given acid and base. For example, if θ is close to 0°, the BDP

presents a character like that of F_1 (electrostatic-charge-transfer). An increase in θ corresponds to a larger dependence on F_2 ; hence the BDP has a greater electrostatic character.

6.2 A general Scale for Hydrogen Bonding

Numerous parameters have been developed to characterize solvent solute interactions. The majority of these are based on calorimetric measurements, that is enthalpy. Recently M. H. Abraham has developed parameters to characterize hydrogen bonding based on Gibb's free energy.

The basicity dependent properties (BDP's) properties were examined for a series of reference acids against reference bases. It was found that a "reasonably general" scale of basicity could be constructed when the characteristic value θ was between 64–73⁰ because the bases showed family independent behavior. This means that when some (BDP)^a (e.g. $\log K$) is plotted against some other (BDP)^b for a series of bases a single straight line is obtained. To be classified as "family independent" all the bases must lie on the line regardless of whether they are oxygen bases, nitrogen bases, etc. Abraham also found family independent behavior for acids; thus, it was possible to develop "reasonably general" scales to characterize both hydrogen bond donors and hydrogen bond acceptors, based on $\log K$ or ΔG^0 .

6.2.1 The α_2^H Parameter

The empirical parameter α_2^H is a measure of a solute's intrinsic ability to donate a hydrogen bond to bases; it is referred to as "a scale of hydrogen-bond acidity".⁵² The parameter is based on the Gibbs free energy ΔG° or the equivalent $\log K$ for the 1 to 1 complex formation between a hydrogen bond donor (HBD) AH and a hydrogen bond acceptor (HBA) B, in which a series of HBD's complex with a reference base in an "inert" solvent such as tetrachloromethane.

The data are organized as a series of $\log K$ values for acids against a given reference base. The series is referred to as 'set' (see Table 6.1). Abraham and coworkers collected 45 sets; i.e., series of $\log K$ values against 45 reference bases. Data were plotted as $\log K(\text{against reference base } x)$ versus $\log K(\text{against reference base } y)$ to provide a single straight line (see Table 6.1). The kinds of lines obtained are depicted in Figure 6.1 which shows that the lines are independent rather than parallel and have a common point of intersection (within a standard deviation of 0.078 log units). In his data analyses, Abraham forced the lines through this common point and termed it the magic point.

Table 6.1. An example of how the data were assembled to determine a general acidity scale. Column 2 is plotted against column 3, . The data were assembled for 45 reference bases.

Acid	$\log K^{\text{BaseX}}$	$\log K^{\text{BaseY}}$
A		
B		
C		
D

Figure 6.1. Plots of $\log K$ for a series of acids against given reference bases vs. $\log K$ for the same series of acids against any other reference base. The lines do not represent actual experimental data and the intersection has been exaggerated.

This feature (the magic point) allowed the 45 data sets to be analyzed in the form of linear equations,

$$\log K^i(\text{series of acids against base 1}) = L_1 \log K_A^H + D_I \quad 6.4$$

$$\log K^i(\text{series of acids against base B}) = L_B \log K_A^H + D_B \quad 6.5$$

The constants L_B and D_B characterize the reference bases. The $\log K_A^H$ values then serve to characterize the hydrogen-bond acids, and hence represent the hydrogen-bond acidity of the acids over all the equations. The $\log K_A^H$ values thus constitute a scale of solute hydrogen-bond donating ability.

The constants (L_B, D_B) characterize the different bases used to measure the equilibrium constant. Over 45 bases have been characterized. What this means is that the ability of two different acids to donate a hydrogen bond may be compared even though the equilibrium constants were determined using two different HBA's, provided the basicities of the two HBA's have been characterized; i.e., provided they have had L_B and D_B values assigned. This is possible through equation 6.6,

$$\log K_A^H = \frac{\log K_B^i - D_B}{L_B} \quad 6.6$$

where $\log K_B^i$ is the measured equilibrium constant using base B, and L_B and D_B are constants for the calibrated base. From the calculated $\log K_A^H$ value, the α_2^H parameter is obtained from equation 6.7.

$$\alpha_2^H = \frac{(\log K_A^H - 1.1)}{4.636} \quad 6.7$$

The constant 1.1 sets the lower limit for hydrogen bonding ability equal to zero . The denominator, 4.636, is a scaling factor. The α_2^H parameter ranges from 0.0 for hydrocarbons and *di*- and *tri*-alkyl amines to ~ 1 for strong acids such as trifluoroacetic acid.

Table 6.2. Reference Bases and their characteristic L_B and D_B values. ^a

	Base	L_B	D_B
1	Pyridine	1.0151	0.0139
2	Triethylamine	1.0486	0.0854
3	Dimethylformamide	1.0719	0.0800
4	HMPA	1.5693	0.6287
5	Acetone	0.7758	-0.2420
6	DMSO	1.2399	0.2656
7	Ethyl acetate	0.7428	-0.2861
8	THF	0.8248	-0.1970
9	Acetonitrile	0.6878	-0.3396
10	Aniline	0.5946	-0.4461

^a Values reported were gathered from the literature. ⁵²

6.2.2 The β_2^H Parameter

Similar to the hydrogen-bonding acidity parameter, α_2^H , the hydrogen-bonding basicity parameter, β_2^H , is based on the change in free energy for the one-to-one complex formed between an acid and a base. It is a measure of a HBA's ability to accept a hydrogen bond. The β_2^H parameter⁵³ is determined from equilibrium constants measured for reaction 6.3 for a series of monomeric HBA's with various reference HBD's. There were 34 data sets used to develop the basicity scale. When data for a series of bases are plotted as $\log K$ (against reference HBD) versus $\log K$ (against any other reference HBD) straight lines are obtained, just as in Figure 6.1 for the α_2^H parameter. Again, a common point of intersection, the magic point, is found at -1.1 .

$$\log K^i(\text{series of bases against acid 1}) = L_I \log K_B^H + D_I \quad 6.7$$

$$\log K^i(\text{series of bases against acid A}) = L_A \log K_B^H + D_A \quad 6.8$$

Through an iterative process – using equations used 6.7, and 6.8- the 34 equations (resulting from the 34 data sets) were solved to produce L_A and D_A for many different HBD's (see Table 6.3). The $\log K_B^H$ values provide a relative measure of a molecule's ability to accept a hydrogen bond. There are over 40 reference acids; thus, if an equilibrium constant is measured for a base with one of the 40 reference acids $\log K_B^H$ may be calculated from equation 6.9.

Table 6.3. Reference Acids and their characteristic L_A and D_A values. ^a

No.	Acid	L_A	D_A
1	phenol	0.946	-0.057
2	4-chlorophenol	1.065	0.074
3	4-bromophenol	1.075	0.084
4	4-nitrophenol	1.299	0.328
5	4-methylphenol	0.907	-0.101
6	2-methylphenol	0.819	-0.198
7	1-naphthol	0.968	-0.034
8	water	0.554	-0.490
9	methanol	0.582	-0.459
10	ethanol	0.538	-0.507
11	butanol	0.516	-0.533
12	t-butyl alcohol	0.496	-0.553
13	indole	0.712	-0.315

^a All values reported were gathered from the literature.⁵³

$$\log K_B^H = \frac{\log K^i - D_A}{L_A} \quad (6.9)$$

The hydrogen-bonding parameter is then calculated using equation 6.10.

$$\beta_2^H = \frac{(\log K_B^H - 1.1)}{4.636} \quad (6.10)$$

where -1.1 restricts the β_2^H to a lower limit of zero, and 4.636 in the denominator compresses the scale so that the strongest base known (HMPA) has $\beta_2^H = 1.00$.

7 Kinetic Solvent Effects

7.1 Introduction

Ingold and coworkers have demonstrated that the absolute rate constants for hydrogen atom abstraction from a substrate by alkoxyl radicals may be dependent⁵⁴ or independent²¹ of the solvent in which the reaction is carried out. The dependence or independence being contingent on the nature of the substrate. For example, the rate constant for hydrogen atom abstraction from cyclohexane by cumyloxyl radicals has been measured at 303 K in several different solvents with varying polarities, dielectric constants, hydrogen bond donor and acceptor properties, and it has been found to be essentially unchanged for all solvents examined (Table 7.1).²¹

Table 7.1. Rate constants for hydrogen atom abstraction from cyclohexane in different solvents by cumyloxyl radicals at 298 K (equation 7.1)a.

	Solvent	$10^{-6} k_H \text{ (M}^{-1} \text{ s}^{-1})^b$
II	tetrachloromethane	1.2
III	chlorobenzene	1.1
IV	benzene	1.2
VIII	acetic acid	1.4
IX	Acetonitrile	1.2
XII	tert-butanol	1.3

^a Rate constants obtained from literature.²¹ ^b Values rounded off to 2 significant figures. The solvents are numbered consistently throughout this thesis. The main list appears in Table 9.1

In sharp contrast, the rate constant for hydrogen atom abstraction from phenol (PhOH) by *tert*-alkoxyl radicals is very much dependent upon the solvent.^{54,55} For example, the rate constant for reaction 7.2 at 298 K is $1.1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ in n-octane, but only $3.6 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ in *tert*-butanol, a decrease of over 2 orders of magnitude (Table 7.2).

Table 7.2. Measured rate constants for hydrogen atom abstraction from phenol by cumyloxyl radicals in different solvents at 298 K (reaction 2).^a

	Solvent	$10^{-7} k^S_{\text{PhOH/RO} \bullet}$ ($\text{M}^{-1}\text{s}^{-1}$)
Ia	n-octane	110
II	tetrachloromethane	86
III	chlorobenzene	48
IV	benzene	28
V	anisole	5.6
VI	methyl formate	1.0
VII	methyl acetate	0.95
VIII	acetic acid	1.8
IX	acetonitrile	5.8
XII	<i>tert</i> -butanol	0.36

^aData acquired from literature.⁵⁵

Because there was no observed KSE for H-atom abstraction from cyclohexane by alkoxyl radicals, reaction 7.1, the KSE found for reaction 7.2 could not be attributed to any change in the reactivity of the alkoxyl radical. It follows that the observed KSE must be due to differences in the substrate / solvent interactions.

7.2 Hydrogen-Bond Donating Properties of CH and OH Functional Groups.

The OH group of phenol is a much stronger hydrogen-bond donor than a CH bond in cyclohexane. Therefore, in hydrogen bond accepting solvents a hydrogen bond will tend to be formed between the hydroxylic hydrogen atom of phenol and a lone pair of electrons on a solvent molecule. The molecules of phenol in the HBA solvent will be found in two states viz., hydrogen bonded and non-hydrogen-bonded, equation 7.3. A saturated hydrocarbon, on the other hand, will not form hydrogen bonds with solvent molecules and will be in a non-hydrogen-bonded state regardless of the solvent, equation 7.4.

7.2.1 A Model for Kinetic Solvent Effects based on Hydrogen Bonding

To rationalize the observed KSE for H-atom abstraction from phenol by the cumyloxyl radical, Ingold and coworkers constructed the simple model shown in Scheme 7.1, where XOH is phenol and S is an HBA solvent. The model relies on four basic assumptions, as follows. ^{54,56}

- i) Each substrate molecule, XOH, can act as a hydrogen bond donor to only a single HBA molecule, S, at any one time.

Scheme 7.1. Kinetic Solvent Effect (KSE) Model

- ii) The magnitude of the equilibrium constant, K^S for the formation of each $\text{XOH}\cdots\text{S}$ hydrogen-bonded complex is essentially independent of the nature (e.g., the dielectric constant) of the surrounding medium.
- iii) Alkoxyl radicals cannot directly abstract the hydroxylic H atom from the $\text{XOH}\cdots\text{S}$ hydrogen-bonded complex (for steric reasons). That is the solvent molecule must be first removed and replaced by an $\text{RO}\bullet$ radical.
- iv) The equilibrium is established rapidly in comparison to the rate of hydrogen atom abstraction.

7.2.2 Kinetic Analysis

The four assumptions in Scheme 7.1 imply that hydrogen atom abstraction from free, i.e., non-hydrogen bonded, XOH is the rate-determining step. A simple kinetic analysis follows:⁵⁴

The total amount of XOH present in the solution is given by,

$$[\text{XOH}]_{\text{total}} = [\text{XOH}] + [\text{XOH}\cdots\text{S}] \quad 7.5$$

and the equilibrium constant for hydrogen bonding between the solvent (S) and the hydroxylic substrate (XOH) is given by,

$$K_{\text{XOH}}^S = \frac{[\text{XOH}\cdots\text{S}]}{[\text{XOH}][\text{S}]} \quad 7.6$$

Thus,

$$[\text{XOH}]_{\text{total}} = [\text{XOH}] (1 + K_{\text{XOH}}^S [\text{S}]) \quad 7.7$$

Consider a non-hydrogen bond accepting solvent (designated *o*), such as a saturated hydrocarbon, for which there will be essentially no interaction with XOH, i.e., the concentration of $[XOH \cdots S]$ is zero, then the *measured* pseudo-first-order-rate constant for hydrogen atom abstraction by radical $Y\bullet$ can be represented by $(k_{XOH/Y\bullet}^o) [XOH]_{total}$ or by $(k_{XOH/Y\bullet}^o)[XOH]$ since $[XOH]_{total} = [XOH]$. For a hydrogen-bond accepting solvent, S, the *measured* pseudo-first order rate constant is given by,

$$(k_{XOH/Y\bullet}^s) [XOH]_{total} = (k_{XOH/Y\bullet}^o) [XOH] \quad 7.8$$

which, on substitution into equation 7.7 yields the second order rate constant,

$$k_{XOH/Y\bullet}^s = \frac{k_{XOH/Y\bullet}^o}{1 + K_{XOH}^s [S]} \quad 7.9$$

where $k_{XOH/Y\bullet}^s$ is the bimolecular rate constant, for reaction 7.2, in solvent S.

7.2.3 Alternative Model Based on Gibb's Free Energy

An alternative model to the one presented above, is based on the Gibb's free energy of activation, $\Delta G^\ddagger$, see Figure 7.1a.⁵⁷ The solvated molecule in solvent II has a lower free energy than in solvent I and the reaction will therefore be slower in solvent II, since

$$k \propto \exp(-\Delta G^\ddagger) \quad 7.10$$

The case where there is no KSE, as for H-atom abstraction from cyclohexane, is shown in Figure 7.1b.

Figure 7.1. The change in Gibb's free energy of the substrate associated with changing the solvent (a), and the case for which there is no solvent-substrate interaction, (b).

7.2.4 The KSE is Independent of the Attacking Radical

The simple kinetic solvent effect model shown in Scheme 7.1 was developed to account for the decrease in the observed bimolecular rate constant for hydroxylic hydrogen atom abstraction by cumyloxyl radicals in HBA solvents.²¹ Ingold and coworkers recognized that this simple treatment of kinetic solvent effects should be applicable to any abstracting radical since the relative amounts of free and of hydrogen bonded XOH depends solely on XOH and the solvent, not on the radical.⁵⁷ The magnitude of the KSE was therefore predicted to be independent of the nature of the radical. In other words for two different radicals, Y• and Z•, it was predicted that,

$$\frac{k_{\text{XOH/Y}\cdot}^{\text{S}}}{k_{\text{XOH/Z}\cdot}^{\text{S}}} = \text{constant} \quad 7.11$$

To explore this prediction the KSE's were measured with a different hydrogen atom abstracting radical, 2,2-diphenyl-1-picrylhydrazyl (DPPH•), which is much less reactive than cumyloxyl radicals.

DPPH• is a commercially available stable, free radical, which does not react with dioxygen. Nevertheless DPPH• can abstract hydrogen atoms from suitable donors. The reaction with phenol is endothermic (ca. 7 kcal/mol) but does occur slowly. In contrast the phenol / cumyloxyl radical reaction is exothermic by ca. 18 kcal/mol and is fast.

Table 7.3. Absolute rate constants for abstraction of phenolic hydrogen from phenol (PhOH) in various solvents at 298K by the cumyloxyl and DPPH radicals. ^a

Solvent		$10^3 k_{\text{PhOH/DPPH}\cdot}^S$ ($\text{M}^{-1}\text{s}^{-1}$)	$10^{-7} k_{\text{PhOH/CumO}\cdot}^S$ ($\text{M}^{-1}\text{s}^{-1}$)
Ia	n-octane	160	110
II	tetrachloromethane	93	86
III	chlorobenzene	59	48
IV	benzene	31	28
V	anisole	7.2	5.6
VIII	acetic acid	3.1	1.8
X	ethyl acetate	1.5	0.81

^a Data were obtained from the literature.⁵⁷

The rate constant for hydrogen atom abstraction from phenol by DPPH $\cdot$ was studied in several solvents⁵⁷ and the data are given in Table 7.3 together with the rate constants for H-atom abstraction by cumyloxyl radicals.⁵⁵ A plot of $\log(k_{\text{PhOH/CumO}\cdot}^S)$ vs. $\log(k_{\text{PhOH/DPPH}\cdot}^S)$ is shown in Figure 7.2. The line in this figure has been drawn with a slope of 1.

Figure 7.2. Plot of $\log(k^S_{PhOH/DPPH})$ for the reaction of phenol with cumyloxyl radicals vs. $\log(k^S_{PhOH/CumO})$ for its reaction with 2,2-diphenyl-1-picrylhydrazyl. The numbers beside the points correspond to the solvents in Table 7.3.

The experimental data fit the prediction remarkably well considering that the rate constants for cumyloxyl and DPPH in any particular solvent differ by a factor of 10, 000, 000, 000! That is,

$$\frac{k_{\text{PhOH/CumO}\bullet}^S}{k_{\text{PhOH/DPPH}\bullet}^S} = 1.0 \times 10^{10} \quad 7.13$$

The relationship indicated in equation 7.13 was further verified using the biologically important antioxidant α -tocopherol (TOH, vitamin E).⁵⁷ Again rate constants for hydrogen atom abstraction by cumyloxyl radicals and DPPH• were measured in various solvents and the plot of $\log(k_{\text{TOH/CumO}\bullet}^S)$ vs. $\log(k_{\text{TOH/DPPH}\bullet}^S)$ gave an excellent linear correlation with a slope of 1. More recently the hypothesis was further verified by Lucarini and coworkers who measured the KSE for hydrogen atom abstraction from α -tocopherol by alkyl radicals.⁵⁸ Barclay and coworkers also found that the magnitude of the KSE to be independent of the abstracting radical by measuring the rate constants for hydrogen atom abstraction from 2,6-di-*tert*-butyl-4-methylphenol, 2,6-di-*tert*-butyl-4-methoxyphenol, and 2,2,5,7,8-pentamethyl-6-hydroxychroman by both DPPH and 2,6-di-*tert*-butyl-4-(4'-methoxyphenyl)phenoxy radicals in several solvents.⁵⁹ Therefore, it can be concluded that the magnitude of the KSE for hydrogen atom abstraction from an XOH hydrogen atom donor is, indeed, independent of the attacking radical.

8 My Objective:

To Predict Ambient Temperature Rate Constants for Hydrogen Atom Abstraction from Any XOH Hydrogen Atom Donor in Any Solvent Using a Bare Minimum of Experimental Measurements

8.1 LFER for Hydrogen Atom Abstraction from Phenol in Different Solvents

In any analysis of kinetic solvent effects on chemical reactions, it is customary to seek a linear relationship between some empirical solvent parameter and the logarithm of the rate constant, i.e., *to seek a linear free energy relationship* (LFER). Considering the kinetic model shown in Scheme 7.1 for the reaction,

it would seem logical that the required solvent parameter for a LFER should provide a measure of the ability of the solvent to accept a hydrogen-bond i.e. the solvent's basicity; Abraham's β_2^H parameter is such a measure and has been used by Ingold and coworkers.⁵⁵ The $\log(k_{\text{PhOH/CumO}\bullet}^S)$ vs. β_2^H LFER for the phenol /cumyloxyl radical reaction is shown in Figure 8.1. The "goodness of fit" is extraordinary; the line has a coefficient of determination (r^2) of 0.98. This excellent LFER is fully consistent with the simple kinetic model shown in Scheme 7.1. That is, it supports the explanation that rate constants for abstraction of the phenolic hydrogen atom from phenol are reduced in HBA solvents because a significant portion of the total added phenol is sequestered by hydrogen bonding.

Figure 8.1. The log of the absolute rate constant for hydrogen atom abstraction by cumyloxyl radicals in various solvents, $\log(k^s_{\text{PhOH/CumO}\cdot})$ vs. β_2^H .

The great importance of this LFER is that it permits the prediction of rate constants in over 250 solvents for which β_2^H values are known. Moreover, it is trivial to measure β_2^H values (*vide infra*), so the list of solvents and solvent mixtures for which $k_{\text{PhOH/CumO}\bullet}^S$ can be reliably predicted -at room temperature- can be extended almost indefinitely. The excellent LFER for $\log(k_{\text{PhOH/CumO}\bullet}^S)$ vs. β_2^H shown in Figure 8.1 has also been mirrored by an excellent correlation of $\log(k_{\text{XOH/CumO}\bullet}^S)$ vs. β_2^H for two other hydroxylic hydrogen atom donors, α -tocopherol and *tert*-butyl hydroperoxide (see Section 9.1).⁶⁰

8.2 Predicting Rate Constants

The correlation of $\log k_{\text{PhOH/RO}\bullet}^S$ with β_2^H and the knowledge that KSE's are independent of the attacking radical opens up the magnificent possibility that many thousands of absolute rate constants could be reliably predicted. Thus, provided rate constants for reaction 8.2

for the same radical, $\text{Y}\bullet$, and the same XOH substrate in two different solvents are available, the LFER, defined by equation 8.3, relating rate constants to β_2^H can be written,

$$\log k_{\text{XOH/Y}\bullet}^S = \log k_{\text{XOH/Y}\bullet}^0 + M_{\text{XOH}} \times \beta_2^H \quad 8.3$$

where k^0 denotes the rate constant for reaction 8.2 in an alkane solvent (non-hydrogen bond accepting, $\beta_2^H = 0$); the β_2^H value refers to solvent S, and M_{XOH} is the slope of the $\log k_{\text{XOH/Y}\bullet}^S$ vs. β_2^H plot. With two kinetic data points, preferably in two solvents with

widely different β_2^H values, equation 8.3 allows rate constants to be predicted in over 250 solvents for which β_2^H values are known. The number of predictions grows (endlessly) when solvent mixtures are considered.

Recall from section 7.2.6 that the magnitude of the KSE is independent of the attacking radical. That is, provided the magnitude of the kinetic solvent effect (M_{XOH}) is known for hydrogen atom abstraction by a particular radical ($Y\bullet$) from a particular hydrogen atom donor (XOH) then the magnitude of the kinetic solvent effect is also known for every other abstracting radical, $Z\bullet$, since they will be the same for all abstracting radicals. Furthermore, if just one absolute rate constant is known for a “new” hydrogen abstracting radical then rate constants may be predicted for the new radical in the other 249 solvents for which β_2^H values are known, always provided that M_{XOH} has been determined previously with some other radical, $Y\bullet$. *If M_{XOH} could be predicted only one absolute rate constant would have to be measured for any new radical $Z\bullet$ to define equation 8.3 and hence to provide of rate constants for the $Z\bullet / XOH$ reaction in a multitude of solvents.*

8.2.1 What Has Been Accomplished in the Following Sections

The ability to predict hundreds of rate constants based on one actual measurement represents an outstanding advance in free radical kinetics. Note that rate constants can be predicted for reactions in solvents that may not even be suitable for experimental measurements; for example, a solvent that absorbs at the laser wavelength required to generate radicals. The predictive power of the simple model shown in Scheme 7.1 and described above would be greatly enhanced if there was some way in which M_{XOH} could

be predicted from some property or combination of properties of XOH. In the following sections, a method is provided to predict M_{XOH} and hence to predict thousands of rate constants with reasonable precision based on one measurement. Also shown is that *reliable predictions can be made for a large family of substituted phenols for which there are no kinetic data, **without** the need for any new experimental measurements!* I consider these achievements to be the most important in my thesis.

9 Reaction of Alkoxyl Radicals With Substituted Phenols

9.1 Introduction

In chapter 8 it was reported that there is a large kinetic solvent effect (KSE) on the absolute bimolecular rate constant for hydrogen atom abstraction by *tert*-alkoxyl radicals from phenol, *tert*-butyl hydroperoxide and vitamin E (α -tocopherol), equation 9.1.

The observed KSE was attributed to the formation of a hydrogen-bonded complex between a solvent molecule –a hydrogen bond acceptor (HBA)- and a substrate molecule –a hydrogen bond donor (HBD). All three substrates have KSE's which appear to be due solely to hydrogen bonding since the rate constants for reaction 9.1 decrease as the solvent becomes a better hydrogen bond acceptor.

The magnitude of a KSE can best be defined as the slope of the plot of $\log(k_{\text{XOH}/\text{RO}}^S)$ vs β_2^H , M_{XOH} . The magnitude of the KSE has been found to be similar for vitamin E ($M_{\alpha\text{-Toc}} = -3.1$), and *tert*-butyl hydroperoxide ($M_{t\text{-BuOOH}} = -3.5$), but was significantly larger for phenol ($M_{\text{PhOH}} = -5.2$) see Figure 9.1.

Values of $\log k_{\text{XOH}/\text{RO}}^S$ should correlate with β_2^H for all hydroxylic *hydrogen atom* donating substrates and the slope (M_{XOH}) should depend upon the ability of XOH to donate a *hydrogen bond* to a HBA. That is, a substrate which is a poor hydrogen bond donor (HBD) is expected to exhibit a smaller KSE than a substrate which is a good hydrogen bond donor.

Figure 9.1. A plot of $\log k^S_{XOH/RO\bullet}$ against β_2^H for α -tocopherol, phenol, and *tert*-butyl hydroperoxide.

Such differences in KSE will *not* depend on the relative *hydrogen atom* donating abilities of the two substrates i.e., will *not* depend on the magnitude of $k_{XOH/RO\bullet}^o$. The ability of XOH to donate a hydrogen bond was expected to depend on its pK_a . Thus, a phenol should be a good HBD if it is relatively acidic; i.e., has a low pK_a , whereas a weakly acidic phenol should be a poor HBD. The parameter, σ^- , is an empirical quantity based on the pK_a 's of phenols. A phenol with a large and negative σ^- has a relatively high pK_a and thus is expected to be a poor HBD and hence to have a small KSE, while a phenol with a large and positive σ^- value will have a low pK_a and is expected to be a relatively good HBD and have a large KSE. There is, therefore an implication that the slopes of the $\log k_{XOH/RO\bullet}^s$ vs. β_2^H plots, M_{XOH} , should correlate with the σ^- parameters of the substituents on the phenol.

In order to explore this prediction I have undertaken a kinetic investigation of hydrogen atom abstraction by alkoxyl radicals from a number of substituted phenols. These include phenol; vitamin E; 2,4,6-trimethylphenol; 4-methoxyphenol; 4-*tert*-butylphenol; 4-chlorophenol; 3,5-dichlorophenol; and 4- α,α,α -trifluorocresol. Phenol and vitamin E were chosen because the kinetic data were already available;^{54,55,57} the other phenols were chosen because of their large range of σ^- values.

9.2 Experiments and Results

9.2.1 Kinetic measurement with alkoxyl radicals

The laser flash photolysis technique described in section 4.2.1 was employed for all phenols except 4-methoxyphenol which had to be excluded because it absorbs at the laser excitation wavelength employed; i.e., 308 nm. *tert*-Butoxyl and cumyloxyl radicals were synthesized from their parent peroxides by 308 nm nano-second laser flash photolysis.

All of the experiments discussed in this section were carried out at room temperature ($23^\circ \pm 2^\circ\text{C}$) in a solvent containing either 0.13 M di-cumyl peroxide, or 0.22 M di-*tert*-butyl peroxide, both of which gave an optical density (O.D.) of 0.3 at 308 nm in a 7mm quartz laser cell.

In the presence of a hydrogen atom donor *tert*-alkoxyl radicals can decay via three distinct pathways (neglecting self-termination):

- i) hydrogen atom abstraction from the phenol (the reaction of interest)

- ii) β cleavage of the alkoxyl radical, reaction 9.4 for *tert*-butoxyl radicals, and reaction 9.4' for cumyloxyl radicals

- iii) reaction with a solvent molecule (SH) if it is able to donate a hydrogen atom

9.2.1.1 Measuring rate constants using di-*tert*-butyl peroxide as a source of alkoxyl radicals

Phenoxyl radicals usually have absorption bands in the 370-505 nm region,⁶¹⁻⁶³ depending upon their substituents. The phenol is used in large excess relative to the *tert*-butoxyl radicals; hence, the signal due to the build-up of the phenoxyl radicals generated via reaction 9.1 will follow pseudo-first-order kinetics according to,

$$k_{\text{exptl}} = k_o + k_H[\text{XOH}] \quad 9.6$$

where k_o corresponds to the combined first and pseudo-first order rate constants for reactions 9.4 and 9.5, and k_{exptl} is the experimental pseudo-first order rate constant derived from the experimental trace according to equation 9.7 (see Figure 9.2)

$$\ln\left(\frac{A_{\infty}}{A_{\infty} - A}\right) = k_{\text{exptl}} \cdot t \quad 9.7$$

where A_{∞} and A are the optical absorptions due to the transient in the plateau region and at time t , respectively. Figure 9.2 shows a typical trace obtained in the case of 4-*tert*-butylphenol, and the inset a plot of the data according to equation 9.7 which has been fitted to a straight line using the least-squares methodology. The slope of this line furnishes the pseudo-first-order rate constant for reaction 9.3.

Figure 9.2. Experimental trace showing the formation of 4-*tert*-butylphenoxy radical monitored at 412 nm in 25:1 benzene : di-*tert*-butyl peroxide solution containing 4.88 mM of the phenol, and (inset) a plot of the data according to equation 9.7.

Figure 9.3. Plot of k_{exptl} according to eq. 9.6 for the reaction of *tert*-butoxyl radical with 4-*tert*-butylphenol (ArOH) in *tert*-butanol.

The k_{exptl} values were measured for at least five different substrate concentrations, spanning approximately one order of magnitude. A plot of k_{exptl} vs. substrate concentration should yield a straight line with a slope equal to the bimolecular rate constant for equation 9.3. Such a plot shown in Figure 9.3. The line in Figure 9.3 does not intersect the origin. The intercept, k_0 is the sum of the first order and pseudo first order rate constants for β -scission of *tert*-butoxyl and hydrogen atom abstraction from the solvent.

9.2.1.2 Measuring rate constants using di-cumyl peroxide as a source of *tert*-alkoxyl radicals

Although obtaining reaction rates by monitoring the growth of phenoxyl radicals is generally straightforward, there are cases where it is difficult, as for example when the extinction coefficient (ϵ) of the phenoxyl radical is weak. Using a *tert*-alkoxyl radical that has a relatively strong absorption in the visible region can overcome this problem.

The cumyloxyl radical- derived from flashing dicumyl peroxide in place of di-*tert*-butyl peroxide has a relatively strong absorption in the visible region ($\lambda_{\text{max}} \approx 485\text{nm}$).^{54,64,65} Therefore, instead of obtaining kinetics of the alkoxyl radical reaction by monitoring the growth of the phenoxyl radical as described above, the kinetics can be obtained by monitoring the decay of the cumyloxyl radical. In the presence of a large excess of a hydrogen atom donor, the decay of the signal due to the cumyloxyl radical will follow pseudo first-order-kinetics according to equation 9.6, k_{exptl}

is the experimental pseudo-first order rate constant derived from the experimental trace according to equation 9.8.

$$\ln\left(\frac{A - A_{\infty}}{A_0 - A_{\infty}}\right) = -k_{\text{exptl}} \cdot t \quad 9.8$$

where A and A_{∞} have their usual meanings, A_0 is the transient's absorption immediately after the laser pulse. Figure 9.4 shows a typical trace for the decay of the cumyloxyl radical in the presence of 2,4,6-trimethylphenol and the inset a plot of the data according to equation 9.8. The bimolecular rate constants measured via the LFP technique are reported in tables 9.1-9.3.

Figure 9.4. Experimental trace showing the decay of cumyloxyl radicals monitored at 485 nm in tetrachloromethane containing 0.13 M dicumyl peroxide, and 2.09×10^{-2} M 2,4,6-trimethylphenol, inset, a plot of the data according to equation 9.8.

Table 9.1. Measured absolute second order rate constants in various solvents, at 296 ± 2 K, for the reaction of phenol, vitamin E, and 4-*tert*-butylphenol with *tert*-butoxyl radicals.

	Solvent	β^H_2	Phenol ^{a, b} $10^{-7} k_H^c$ $M^{-1}s^{-1}$	Vitamin E ^a $10^{-8} k_H^c$ $M^{-1}s^{-1}$	4- <i>tert</i> - butylphenol $10^{-8} k_H^c M^{-1}s^{-1}$
I ^c	n-pentane	0.0	110 ^d	99	-
II	tetrachloromethane	0.05	86	42	19.1
III	chlorobenzene	0.09	48	36	12.9
IV	benzene	0.14	28	31	8.72
V	anisole	0.26	5.6	20	2.30
VI	methyl formate	0.38	1.0	-	0.460
VII	methyl acetate	0.40	0.95	3.0	-
VIII	acetic acid	0.42	1.8	7.7	0.602
IX	acetonitrile	0.44	0.58	9.4	0.407
X	ethyl acetate	0.45	0.81	2.9	-
XI	γ -valerolactone	0.45	-	1.65	-
XII	<i>tert</i> -butanol	0.49	0.36	1.80	0.193

^a Values gathered from the literature: phenol⁵⁵, vitamin E.⁵⁷ ^b Measured using cumyloxyl radicals. ^c Estimated error, $\pm 20\%$.⁶¹ ^d Measured in n-octane. ^e The numbers correspond to the data points in Figure 9.6-9.8, the numbering is the same used through this thesis.

Table 9.2. Measured absolute second order rate constants in various solvents, at 296 ± 2 K, for the reactions of p- α,α,α -trifluorocresol; 2,4,6-trimethylphenol; and 4-chlorophenol with cumyloxyl radicals.^a

	Solvent	β_2^H	4- α,α,α - trifluoro-cresol $10^{-7} k_H$ ($M^{-1}s^{-1}$)	2,4,6- trimethyl- phenol $10^{-8} k_H$ ($M^{-1}s^{-1}$)	4-chloro- phenol $10^{-7} k_H$ ($M^{-1}s^{-1}$)
I	pentane	0.0	85.0	21.1	230
II	CCl ₄	0.05	71.0	16.1	110
III	chlorobenzene	0.09	17.2	-	-
IV	benzene	0.14	13.0	-	40.4
V	anisole	0.26	2.10	4.86	6.87
VI	methyl formate	0.38	0.389	1.20	1.89
VIII	acetic acid	0.42	0.542	-	-
IX	acetonitrile	0.44	0.210	0.834	0.789
XII	tert-butanol	0.49	0.102	-	-

^a Estimated error $\pm 20\%$.⁶¹

Table 9.3. Measured absolute second order rate constants in various solvents, at 296 ± 2 K, for the reaction of 3,5dichlorophenol with cumyloxyl radicals.^a

	Solvent	β_2^H	$10^{-7} k_H$ ($M^{-1}s^{-1}$)
I	pentane	0.0	94.0
II	tetrachloromethane	0.05	87.5
III	chlorobenzene	0.09	29.4
IV	benzene	0.14	16.1
V	anisole	0.26	3.47
VI	methyl formate	0.38	0.594

^a Estimated error $\pm 20\%$.⁶¹

9.2.2 Measuring Rate Constants via Competitive Kinetics:

The LFP technique used to acquire absolute bimolecular rate constants for hydrogen atom abstraction from phenols by alkoxyl radicals was suitable for most phenols. However, the method could not be used for p-methoxyphenol because this compound absorbs at the laser wavelength, so kinetic data were gathered by competition methods. The theory has been described in detail in section 4.3, the application to the present case is reported here.

Cumyloxyl radicals were generated by thermal decomposition of their parent hyponitrite.

Scheme 9.1. Thermal decomposition of dicumyl hyponitrite (DCHP) and the affect of the solvent cage.

The reactions of cumyloxyl radicals derived from dicumyl hyponitrite (DCHP) with the hydrogen atom donor (XOH) were carried out at room temperature in the dark in sealed reaction vessels made of Pyrex for a period of time (10 days) that allowed >99% of the hyponitrite to decompose. The duration of the experiment was determined by the half-life of dicumyl hyponitrite which can be calculated from the Arrhenius equation reported by G. D. Mendenhall *et al* ⁶⁶

$$\log k(T) = \log A_{obsd} - \frac{E_{obsd}}{2.303RT} \quad 9.10$$

viz: $\log A = 14.97$, $E_{obsd} = 1.13 \times 10^5$ J/mol. At 298 K the first-order rate constant for the thermal decomposition of dicumyl hyponitrite can be calculated to be ca. $1.19 \times 10^{-5} \text{ s}^{-1}$, which yields a half-life of 16 h, i.e., 15 half-lives in 10 days.

In order to treat the reaction as a pseudo-first-order process, the reagent concentrations used were such that no more than 5% of the phenol could react with alkoxyl radicals. This was achieved by using a hyponitrite to phenol concentration ratio of 1: 40, noting that almost two alkoxyl radicals are furnished for every molecule of DCHP that decomposes. The reactions were performed with at least 5 different phenol concentrations, the ratio of hyponitrite to phenol being kept the same for all experiments.

Table 9.4 Unimolecular rate constants for the β -scission of the cumyloxyl radical in several different solvents at 303 K. ^a

	Solvent	$10^{-5} k_{\beta} \text{ (s}^{-1}\text{)}$
II	tetrachloromethane	2.6 ₃
III	chlorobenzene	5.5 ₄
IV	benzene	3.7 ₅
VIII	acetic acid	19.6
IX	acetonitrile	6.3 ₃
XII	tert-butanol	5.8 ₄

^a Taken from the literature.²¹

Figure 9.5. A plot of the ratio of cumyl alcohol to acetophenone against the concentration of 4-methoxyphenol in acetic acid at 298 ± 2 K.

After the reaction was complete the absolute concentrations of cumyl alcohol and acetophenone were measured by GC/FID. A plot of the product ratio [cumyl alcohol] / [acetophenone] against the phenol concentration, equation 9.11,

$$\frac{[\text{cumyl alcohol}]}{[\text{acetophenone}]} = \frac{k_{XOH}}{k_{\beta}} [XOH] \quad 9.11$$

has a slope equal to the ratio of the rate constants for hydrogen atom abstraction, reaction 9.3 to β -scission of the cumyloxyl radical. Since k_{β} is known, see Table 9.4,²¹ the absolute value of k_{XOH} is obtained as the product of the slope and k_{β} . An example a plot according to equation 9.11 is given in Figure 9.5.

9.2.3 Measuring the rate constant (k_{β}) for the β -scission of the cumyloxyl radical in anisole

As described in section 9.2.2, the rate constant for β -scission (k_{β}) of the cumyloxyl radical is solvent dependent; therefore, absolute bimolecular rate constants may be obtained via the competitive technique in different solvents only if k_{β} is known or measured in each solvent of interest. The value of k_{β} is available in several different solvents, but not for anisole one of the solvents used in this study. The method for experimentally measuring k_{β} is very similar to the competition procedure described for measuring the rate constant for reaction 9.3, except that the hydrogen atom donating substrate is cyclohexane because the rate constant for reaction 9.12 is solvent independent,²¹ and thus requires no additional measurements.

A plot of

$$\frac{[\text{cumyl alcohol}]}{[\text{acetophenone}]} \text{ vs. } [c\text{-C}_6\text{H}_{12}] \quad 9.13$$

has a slope equal to $\frac{k_H}{k_\beta} = 1.2 \times 10^6 \text{ M}^{-1}\text{s}^{-1} / k_\beta$, so that k_β can readily be determined.

Table 9.5 Unimolecular rate constants for the β -scission of the cumyloxyl radical in anisole at 303 $\pm$ 2K, measured via competition methods.

	Solvent	k_H/k_β (M^{-1})	$k_\beta \times 10^5 \text{ s}^{-1}$	Minimal Mass Balance ^a	Corrected Mass Balance ^b
V	anisole	3.3 ₄	3.5 ₉	89	100

^a Based on measured concentrations of cumyl alcohol and acetophenone. ^b Corrected by calculating the amount of dicumyl peroxide produced by in cage collapse (see text).

9.2.4 Mass Balances for Competitive Kinetics and the “Cage effect”

The kinetic data gathered via the competitive kinetic technique for 4-methoxyphenol are reported in Table 9.6 where it can be seen that the minimal mass balances (based on hyponitrite used and the absolute concentrations of acetophenone and cumyl alcohol produced) are good but are all below 100%. This is readily understood in terms of Scheme 9.1 which shows that there is also an in cage process^{67,68} which produces dicumyl peroxide. This does not effect the determination of k_H / k_β .

The concentration of dicumyl peroxide was not measured because of its thermal instability. The efficiency of the in cage combination of alkoxyl radicals increases with increasing solvent viscosity.⁶⁷ For this reason better minimal mass balances were obtained in the low viscosity solvents, chlorobenzene, benzene, and acetonitrile; (viscosities at 298 K are ~0.715 cp, 0.608 cp, and 0.345 cp respectively)⁶⁹ than solvents of high viscosity, anisole (~ 1.30cp) and acetic acid (~ 1.15cp).

Table 9.6. Relative rates in various solvents measured by competitive kinetics, at 298 ± 2 K, for the reaction of cumyloxyl radicals, generated by the thermolysis of dicumyl hyponitrite with p-methoxyphenol.

	Solvent	k_H/k_β (M^{-1})	$10^{-8} k_H$ ($M^{-1}s^{-1}$) ^a	β_2^H	Minimal Mass Balance % ^{b, c}	Corrected Mass Balance ^d
III	chlorobenzene	7850	36.3	0.09	94(2.4) ^d	102
IV	benzene	9718	30.3	0.14	95(5.7)	102
V	anisole	5135	15.3	0.26	90(4.5)	101
VIII	acetic acid	120	1.96	0.42	90(5.7)	100
XI	acetonitrile	216	1.08	0.44	97(3.8)	101

^a Calculated from k_H/k_β using k_β values that were 1/1.2 (=0.83) times those given in Tables 9.4 and 9.5 to allow for the 5° C difference in the temperatures at which k_H/k_β and k_β were determined, viz., 298 and 303 K, respectively. ^b Based on measured concentrations of cumyl alcohol and acetophenone. ^c Mass balances are the mean value for the 6 or more data points in each solvent. ^d Numbers in parentheses are the standard deviation on the mean. ^e See text.

Minimal mass balances were corrected by calculating the amount of dicumyl peroxide expected to be produced in each solvent based on its viscosity using experimental data for the in-cage formation of di-*tert*-butyl peroxide in the analogous decomposition of di-*tert*-butyl hyponitrite as reported by Kiefer and Traylor.⁶⁸ A double reciprocal plot of the fraction of cage collapse vs. viscosity was fitted to a third order polynomial (see appendix A.1). The ratio of *cage escape* to *cage collapse* was calculated for each solvent and the corrected mass balances were all very close to 100%, see Table 9.6.

Figure 9.6. $\log k^s_{\text{PhOH/CumO}\cdot}$ vs. β_2^H for hydrogen atom abstraction from phenol in different solvents.

Figure 9.7. $\log k^S_{\alpha\text{-toc}/t\text{-BuO}\cdot}$ vs. β_2^H for hydrogen atom abstraction from α -tocopherol in different solvents.

Figure 9.8. $\log k^S_{ArOH/CumO\cdot}$ vs. β_2^H for hydrogen atom abstraction from 4-*tert*-butylphenol in different solvents.

Figure 9.9. $\log k^s_{\text{ArOH/t-BuO}\cdot}$ vs. β_2^H for hydrogen atom abstraction from 4-chlorophenol in different solvents.

Figure 9.10. $\log k_{ArOH/CumO\cdot}^S$ vs. β_2^H for hydrogen atom abstraction from 4- α,α,α -trifluorocresol in different solvents.

Figure 9.11. $\log k^S_{ArOH/CumO\cdot}$ vs. β_2^H for hydrogen atom abstraction from 3,5-dichlorophenol in different solvents.

Figure 9.12. $\log k^s_{ArOH/CumO\cdot}$ vs. β_2^H for hydrogen atom abstraction from 2,4,6-trimethylphenol in different solvents.

Figure 9.13. $\log k^s_{\text{ArOH/CumO}^\bullet}$ vs. β_2^H for hydrogen atom abstraction from 4-methoxyphenol in different solvents.

9.3 Discussion

Large kinetic solvent effects were observed for hydrogen atom abstraction from all phenols examined, see Tables 9.1-9.3 and 9.6. These rate constants decrease as the solvent becomes a better HBA, i.e., as its β_2^H value increases. For all phenols studied, the plots of $\log k_{XOH/RO}^S$ vs. β_2^H gave excellent straight lines, see Figures 9.6-9.13. The linear coefficients of determination are exceptionally high ($r^2 \geq 0.98$) for all phenols, except 4-methoxyphenol ($r^2 = 0.95$, studied by product analysis rather than LFP) and α -tocopherol ($r^2 = 0.86$, where many of the $k_{XOH/RO}^S$ values approach the diffusion-controlled limit). The equation of the line for each phenol is reported in Table 9.7 together with their coefficients of determination and the $\Sigma\sigma^-$ values for the phenols.

Table 9.7. Equations of the lines obtained from plotting $\log k_{XOH/RO}^S$ vs. β_2^H for all of the phenols studied along with the phenols' $\Sigma\sigma^-$ values.

No.	Compound	M_{XOH}^a	Intercept $\log k_{XOH/RO}^O$	r^2	$\Sigma\sigma^-$
1 ^b	α -tocopherol	-3.0	9.9 ₁	0.86	-0.83 ^c
2	2,4,6-trimethylphenol ^c	-3.2 ₃	9.3 ₂	0.98	-0.39 ^c
3	4-methoxyphenol	-4.3 ₁	10. ₂	0.95	-0.26
4	4-tert-butylphenol	-4.4 ₆	9.5 ₂	0.98	-0.13
5	phenol	-5.20	9.1 ₄	0.98	0.0
6	4-chlorophenol	-5.5 ₄	9.3 ₄	0.99	0.19
7	4- α,α,α -trifluorocresol	-5.8 ₈	8.9 ₄	0.98	0.65
8	3,5-dichlorophenol	-5.9 ₉	9.0 ₆	0.98	0.74

^a Slope of the line i.e. $\log k_{XOH/Y}^S$ vs β_2^H . ^b The numbers correspond to the data points in Figure 9.14, the numbering is the same used throughout this thesis. ^c Calculated using the relation found by M. Jonsson *et al* for σ^+ i.e., $\sigma_O^- = 0.66\sigma_P^-$.⁷⁰

Figure 9.14. Slope of $\log(k^s_{ArOH / RO.})$ vs. β_2^H ; i.e., M_{XOH} , plotted against $\Sigma\sigma^-$. The numbers besides the points correspond to the entries in Table 9.7.

The slopes of the $\log k_{XOH/RO\bullet}^s$ vs. β_2^H plots are substrate dependent and range from -3.0 for vitamin-E to -6.0 for 3,5-dichlorophenol. These slopes are a measure the sensitivity of the rate constants to changes in the HBA properties of the reaction media. Thus, for vitamin E a change in solvent over the entire range of HBA activities from pentane, ($\beta_2^H = 0.00$) to HMPA ($\beta_2^H = 1.00$) would reduce the rate constant for hydrogen atom abstraction by about one thousand (10^3) and for 3,5dichlorophenol the rate constant would decrease by a factor of one million (10^6). Recall the magnitude of these KSE's will not depend on the nature of the attacking radical.

To determine whether M_{XOH} correlates with the pK_a of the phenols, values of M_{XOH} have been plotted against $\Sigma\sigma^-$ parameter for all phenols examined in Figure 9.14 (see next page). The line has a slope -2.0 and a coefficient of determination (r^2) of 0.89 indicating that M_{XOH} correlates poorly with $\Sigma\sigma^-$, i.e. with pK_a . This would appear to imply that there is not a very good correlation between the ability of a phenol to act as a hydrogen bond donor and its pK_a . This point is illustrated in Appendix A.2.

10 Kinetic Solvent Effects Correlated with Abraham's Relative

Acidity Parameter, α_2^H

10.1 Introduction

The kinetic investigation of hydrogen atom abstraction from substituted phenols by alkoxyl radicals confirmed that the absolute bimolecular rate constant for equation 10.1 is solvent dependent.

Specifically, for all phenols studied $\log k_{\text{XOH}/\text{RO}\cdot}^s$ correlated with β_2^H and the rate constants decreased as β_2^H increased. The slopes of these lines, M_{XOH} , depended on XOH but correlated only poorly with $\Sigma\sigma^-$.

Abraham's α_2^H parameters (see section 6.2.1), are a measure of the relative ability of a solute to act as a HBD. Thus, α_2^H might well provide a better correlation with M_{XOH} than $\Sigma\sigma^-$. The α_2^H parameter has an added advantage: it should apply to all XOH hydrogen atom donors regardless of whether their ability to donate a hydrogen bond is influenced by steric or electronic factors (or both) and regardless of whether or not they are phenols.

The subscripts of M need to be defined explicitly. M_{RXH} is the slope of the $\log(k_{\text{RXH}/Y\cdot}^s)$ vs. β_2^H plot, where RXH refers to any hydrogen atom donor; M_{ArOH} will represent phenols, and M_{XOH} will refer to *any* substrate that has the labile hydrogen atom

attached to oxygen; cases where M is given with no subscript means that the substrate is understood from the context.

The α_2^H parameters for phenol, 4-methoxyphenol, 4- α,α,α -trifluorocresol, 3,5-dichlorophenol, and 4-*tert*-butylphenol were measured and found to be in good agreement with the literature.⁵² Values of $M_{A/OH}$ were plotted against α_2^H for these five phenols and for 2,4,6-trimethylphenol, and 4-chlorophenol. An excellent linear correlation was obtained (Figure 10.3) which allowed α_2^H -values to be predicted for vitamin E and *tert*-butyl hydroperoxide from their M_{XOH} values. These predicted values were: vitamin E⁵⁷ $\alpha_2^H=0.363$ and *tert*-butyl hydroperoxide⁵⁴ $\alpha_2^H=0.425$. I then measured the α_2^H values for these two compounds and obtained values of 0.370 and 0.442, respectively, in excellent agreement with the predictions.

10.2 Experiments and Results

The equilibrium constants for 1:1 complex formation between a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) were measured by infrared spectroscopy. Solutions of the hydrogen bond acceptors were prepared in tetrachloromethane which had been distilled over phosphorus pentoxide to remove any traces of water. A Bomem Fourier Transform Infrared spectrophotometer (120 series) was used to measure O-H band intensities. The effective slit width was 4 cm⁻¹. Peak heights were measured relative to the baseline. The phenol concentrations were in the range of 1 mmol– 32 mmol. Measurements were made using a CaF₂ cell with ~ 2.5mm path length. DMSO was the base (HBA) used in all experiments. The reaction scheme is shown in Scheme 10.1.

$$K_{\text{eq}} = \frac{x}{(a-x)(b-x)}$$

Scheme 10.1. Reaction scheme for the 1 to 1 complex formation of a hydrogen bond donor (XOH) and a hydrogen bond acceptor (HBA) and the expression for the equilibrium constant.

When DMSO was added to the solution containing the phenol the sharp peak observed at $\sim 3600 \text{ cm}^{-1}$ (Figure 10.1a) decreased in intensity and a new broad peak due to the $[\text{DMSO} \cdots \text{HOX}]$ complex appeared in the $\sim 3200 \text{ cm}^{-1}$ region (Figure 10.1b). The peak height of the non-hydrogen bonded OH stretching vibration at $\sim 3600 \text{ cm}^{-1}$ was used to calculate the concentration of the free XOH using the Beer-Lambert Law and a standard calibration curve. A calibration curve is important for two reasons: i) to ensure that the concentrations used are in the linear region of the Beer-Lambert law, and ii) to ensure dimerization of the HBD does not occur.

Figure 10.1. FT-IR spectra of phenol (1.18 mmol) in tetrachloromethane (a) and in tetrachloromethane with 15.0 mmol DMSO (b).

The equilibrium constant for complex formation is equal to the slope of the plot

$$\frac{[\text{H-bonded complex}]}{[\text{XOH}]_{\text{free}}} \text{ vs. } [\text{DMSO}]_{\text{free}} \quad 10.2$$

The concentration of the hydrogen bond complex (x in Scheme 10.1) is calculated from the concentration of the free XOH ($[\text{XOH}]_{\text{free}}$ or a-x in Scheme 10.1) in solution. The concentration of non-H-bonded HBA in solution ($[\text{DMSO}]_{\text{free}}$, or b-x in Scheme 10.1) is calculated in the same manner. A typical graph is shown in Figure 10.2.

Figure 10.2. A graph in the form of equation 10.2. The slope is equal to the equilibrium constant, K_{eq} , for the 1 to 1 hydrogen-bond complex formation between DMSO and phenol in tetrachloromethane at room temperature (20 ± 2 °C).

Table 10.1. Measured equilibrium constants, K_{eq} , for 1:1 complex formation between some hydrogen bond donors and the hydrogen bond acceptor (DMSO) in tetrachloromethane at 20 ± 2 °C.

	Hydrogen Bond Donor	$K_{eq} \text{ M}^{-1}$	α_2^H	α_2^H (literature) ⁵²
3	4-methoxyphenol	119	0.550	0.573
4	4-tert-butylphenol	153	0.571	0.558
5	phenol	197	0.590	0.596
7	4- α,α,α -trifluorocresol	672	0.680	0.724
8	3,5-dichlorophenol	1216	0.728	0.774

The equilibrium constants for 1:1 complex formation between DMSO and various hydrogen bond acceptors are reported in Table 10.1.

The α_2^H parameters were calculated using equation 10.2 and 10.3.

$$\log K^i = L_B \log K_A^H + D_B \quad 10.2$$

Where $\log K^i$ is the measured equilibrium constant and L_B and D_B are parameters that characterize the base, for DMSO $L_B=1.2399$ and $D_B=0.2656$. Equation 10.3 furnishes the

α_2^H parameter,

$$\alpha_2^H = \frac{\log K_A^H + 1.1}{4.636} \quad 10.3$$

Table 10.1 lists the α_2^H parameters determined from this study and, for comparison, the α_2^H values available from the literature.⁵²

10.3 Discussion

The expectation that M_{ArOH} would correlate with the ability of ArOH to donate a hydrogen bond, as described by the α_2^H parameter for ArOH, is borne out by the plot shown in Figure 10.3. The straight line in this figure has been drawn using the data from Table 10.2 and the data point (0,0) *vide infra*.

Table 10.2. α_2^H parameters and the slopes, M_{ArOH} , determined in section 9.2.

	phenol	α_2^H ^a	M_{ArOH}
2 ^c	2,4,6-trimethylphenol	0.374 ^b	-3.23
3	4-methoxyphenol	0.550	-4.28
4	4-tert-butylphenol	0.571	-4.45
5	phenol	0.590	-5.20
6	4-chlorophenol	0.670 ^b	-5.54
7	4- α,α,α -trifluorocresol	0.683	-5.88
8	3,5-dichlorophenol	0.728	-5.93

^a No units. ^b Taken from the literature.⁵² ^c The numbers correspond to the data points in Figure 10.3, the numbering is the same used in Table 9.7 and throughout this thesis.

Figure 10.3. Plot of M_{ArOH} vs. α_2^H . The numbers beside the data points correspond to the phenols in Table 10.2.

Figure 10.3 has a slope of -8.28 and an intercept of 0.00, as determined via the *least squares* methodology. The coefficient of determination of the line (r^2) is 0.988.

The line in Figure 10.3 intercepts the origin as it should. Recall, there is no KSE on hydrogen atom abstraction from alkanes,²¹ (e.g., $M_{C_6H_{12}}$ is equal to zero) and the α_2^H value is zero for alkanes and other substrates unable to donate a hydrogen bond. Therefore, the data point $\{(M_{C_6H_{12}}, \alpha_2^H) = (0,0)\}$ is a boundary on equation 10.4. Thus, this equation would seem to be applicable to phenols *and* alkanes. Its applicability to other substrates will be considered later.

$$M_{RXH} = -8.2_8 \times \alpha_2^H \quad 10.4$$

To test equation 10.4 the α_2^H parameters were calculated for vitamin E and *tert*-butyl hydroperoxide from their M_{XOH} values^{54,55,57} since these α_2^H values were not available in the literature. The calculated α_2^H values agree very well with the values measured by IR (with DMSO as a base) see Table 10.3.

Table 10.3. Calculated (from M_{XOH}) and measured α_2^H parameters for vitamin E and *tert*-butyl hydroperoxide using equation 10.4.

XOH		K_{eq}^{DMSO}	α_2^H Predicted	α_2^H Measured	M_{XOH}
1	α -tocopherol	10.7	0.363	0.370	-3.01 ^a
9	$(CH_3)_3COOH$	27.8	0.425	0.442	-3.52 ^b

^a Kinetic data gathered from the literature.⁵⁷ ^b Kinetic data used to determine this value are given in appendix A.3 and were gathered from the literature.⁵⁴

Figure 10.4. A graph of M_{XOH} against α_H^2 . The numbers beside the points correspond to hydrogen atom donors in Tables 10.2 and 10.3.

The agreement between the calculated and measured α_2^H values for *tert*-butyl hydroperoxide is of special interest because it further demonstrates the applicability of equation 10.4. Thus, it seems likely that this equation may be general for all hydrogen atom donating substrates irrespective of whether they can (phenols and *tert*-butyl-hydroperoxide) or cannot (cyclohexane) act as hydrogen bond donors.

The least squares equation of the line (Figure 10.4) for all the experimental data, i.e., Tables 10.2 and 10.3 is given by

$$M_{XOH} = -8.3_2 \times \alpha_2^H \quad 10.5$$

The coefficient of determination of the line (r^2) is 0.987.

2-Methoxyphenol and aniline were used to explore further the versatility of equation 10.5. Their α_2^H values, the predicted values of M_{ArXH} and the M_{ArXH} values determined from experimental kinetic data for these two compounds are summarized in Table 10.4.

Table 10.4. Predicted and measured M values for 2-methoxyphenol and aniline.^a

Substrate	α_2^H ^b	M (Predicted)	M (Measured)
10 2-methoxyphenol ^c	0.261	-2.17	-1.9 ₈
11 Aniline ^d	0.264	-2.20	-2.2 ₂

^a The data used to determine M for aniline and 2-methoxyphenol are given in appendices A.4 and A.5 respectively. ^b Literature values.⁵² ^c Kinetic data for 2-methoxyphenol were gathered from the literature.⁷¹ ^d Kinetic data for aniline were gathered from the literature.⁵⁵

The predicted and measured values of M in Table 10.4 are in excellent agreement. Figure 10.5 shows a plot of M_{RXH} versus α_2^H for all eleven substrates considered above.

2-Methoxyphenol is of special interest because it has an intramolecular hydrogen bond⁷² and a relatively small KSE.⁷¹ The small KSE has been attributed to the formation enthalpy of the hydrogen bond formed between the OH of the phenol and a HBA solvent molecule.⁷¹ The intramolecular hydrogen bond of 2-methoxyphenol has an enthalpy of formation ($\Delta H_{\text{intra-HB}}$) of $-4.3 \text{ kcal mol}^{-1}$,⁷³ thus it can be calculated that in a non-HBA solvent such as a saturated hydrocarbon at 298 K $> 99.9\%$ of the phenol exists in the intramolecular hydrogen bonded form.⁷¹ The intermolecular hydrogen bonding of 2-methoxyphenol with ethyl acetate has an enthalpy of $-2.8 \text{ kcal mol}^{-1}$ which may be compared to $-4.5 \text{ kcal mol}^{-1}$ for intermolecular hydrogen bonding between 4-methoxyphenol and ethyl acetate. Thus, 2-methoxyphenol is a relatively poor inter-HBD and as a consequence it has a small $K_{\text{eq(inter)}}$, reflected by its relatively low α_2^H value, which is also consistent with a small KSE.

Aniline is also of interest because it demonstrates that equation 10.5 is applicable to substrates that are very weak HBD's and to substrates in which the labile hydrogen atom is attached to a heteroatom other than oxygen or carbon.

Figure 10.5. A graph of M_{RXH} against α_2^H for all the substrates considered in this section.

The ability to calculate the values of M_{RXH} from α_2^H values allows rate constants to be predicted with great ease. Consider equation 10.6.

$$\log k_{RXH/Y\bullet}^S = \log k_{RXH/Y\bullet}^o + M_{RXH} \times \beta_2^H \quad 10.6$$

At least two absolute rate constants, in two solvents with known and reasonably different β_2^H values, are required to define the line; however, upon substituting equation 10.5 into 10.6 we obtain:

$$\log k_{RXH/Y\bullet}^S = \log k_{RXH/Y\bullet}^o - 8.3_2 (\alpha_2^H \times \beta_2^H) \quad 10.7$$

To define equation 10.7 only one absolute bimolecular rate constant is required for the reaction of interest in any solvent. The parameters, β_2^H and α_2^H , are obtained from the literature or, if need be, are measured by infrared spectroscopy. Hence, with the ability to calculate the slope of $\log(k_{RXH/Y\bullet}^S)$ vs. β_2^H the kinetic information required to predict rate constants in hundreds of solvents has been reduced to one single measured rate constant in any solvent.

There are two advantages to correlating M_{XOH} with α_2^H rather than σ^- or pK_a . First and foremost, the correlation is more than adequate to allow M_{RXH} to be reliably predicted through equation 10.5. Second, α_2^H is a general parameter which has been or can be determined with extreme ease for any hydrogen bond donor. The plot of M_{RXH} versus σ^- is necessarily limited to phenols and the measurement of pK_a 's for phenols can be tedious and is often unreliable because it may involve non-reversible cyclic

voltametry.⁷⁴ In contrast, the determination of α_2^H requires only a few simple I.R. measurements. This means that the magnitude of the kinetic solvent effect, M_{RXH} , for some “new” RXH can be predicted, *without a single kinetic measurement*. Then, one single absolute kinetic measurement with the chosen hydrogen atom abstracting radical in any solvent will provide absolute rate constants in any and all other solvents.

It is clear that the relative acidity parameter α_2^H can be predicted from the M_{RXH} value of the substrate or, *more importantly for the purposes of thesis, the M_{RXH} value for a hydrogen atom donor can be predicted from its α_2^H value.*

10.4 Conclusions

The magnitude of the KSE, M_{RXH} , for hydrogen atom abstraction correlates - linearly- extremely well with Abraham's α_2^H values, which characterize the hydrogen atom donors ability to donate a hydrogen bond. The correlation allows M_{RXH} to be reliably predicted, from which rate constants may be predicted for a RXH / Y^{*} reaction in hundreds of solvents. The correlation is valid for phenols, alkyl hydroperoxides, aromatic amines, and alkanes. In addition a new method has been provided that allows the accurate determination of α_2^H values, and it is emphasized that it does not require a laser flash apparatus, since the kinetic measurements may be done with DPPH^{*} and a spectrophotometer; this could be a valuable procedure for very weak acids.

11 Hydrogen Atom Abstraction From Substituted Phenols by DPPH in Heptane

11.1 Introduction

The simple KSE model presented in chapter 7.2.1 predicts that the rate constant for hydrogen atom abstraction from RXH will depend on the hydrogen bond donating ability of RXH and the hydrogen bond accepting ability of the solvent. The LFER, equation 11.1, not only provides compelling evidence in favor of the KSE model, but also furnishes an equation that allows rate constants to be easily and accurately predicted:

$$k_{\text{RXH/Y}\cdot}^{\text{S}} = k_{\text{RXH/Y}\cdot}^{\text{O}} + M_{\text{RXH}} \times \beta_2^{\text{H}} \quad 11.1$$

In addition, the simple KSE model forecasted that the magnitude of M_{RXH} would depend on the ability of RXH to donate a hydrogen bond, as described by its α_2^{H} values. This dependence of M_{RXH} on α_2^{H} was proven in chapter 10 and equation 11.2 was discovered:

$$M_{\text{RXH}} = -8.3_2 \times \alpha_2^{\text{H}} \quad 11.2$$

When equation 11.1 and 11.2 are combined we obtain:

$$\log k_{\text{RXH/Y}\cdot}^{\text{S}} = \log k_{\text{RXH/Y}\cdot}^{\text{O}} - 8.3_2 (\alpha_2^{\text{H}} \times \beta_2^{\text{H}}) \quad 11.3$$

This equation means that absolute bimolecular rate constants can be accurately predicted provided one rate constant is known ($k_{\text{RXY/Y}\cdot}^{\text{S}}$ or $k_{\text{RXY/Y}\cdot}^{\text{O}}$) and the appropriate α_2^{H} and β_2^{H} parameters are known (or measured). If this one required rate constant could be predicted then absolutely no kinetic measurements on RXH would be required. I have not totally succeeded in achieving this goal, but I have succeeded in predicting

$\log k_{\text{ArOH}/Y\bullet}^o$ for some “new” phenol provided I have one value for $k_{\text{ArOH}/Y\bullet}^S$ for each of two other different phenols (ArOH) in any solvent (and not necessarily the same solvent).

The objectives of this chapter are two fold. First, to test equation 11.3. The rate constant for the 4-methoxyphenol / DPPH $\bullet$ reaction will be predicted in heptane, $\beta_2^H = 0.00$, based on the rate constant for the same reaction in DMSO, $\beta_2^H = 0.78$, and the predicted value will be compared with the experimental value.

DMSO and heptane were chosen as the two solvents because the predicted and the measured rate constants are in solvents that span 78% of the entire β_2^H scale. Second, a rate constant will be measured for the reaction of a different phenol with DPPH in heptane and will be used in conjunction with the predicted rate constant for the 4-methoxyphenol / DPPH reaction in heptane to predict $\log(k_{\text{ArOH}/\text{DPPH}\bullet}^o)$ for any “new” ArOH without the need for any further kinetic measurements.

Rate constants are often described in terms of the Arrhenius equation

$$\log k = \log A - \frac{E_a}{2.303RT} \quad 11.5$$

I wanted to be able to predict rate constants for hydrogen atom abstraction by the same radical, Y $\bullet$, over the entire family of substituted but sterically unhindered or only slightly hindered phenols. The pre-exponential factors for such closely related reactions will be essentially identical. Therefore,

$$\log \left(\frac{k^{\text{ArOH}}}{k^{\text{PhOH}}} \right) \propto -E_a^{\text{ArOH}} + E_a^{\text{PhOH}} \quad 11.6$$

The activation energy is related to the change in enthalpy for a related family of hydrogen atom abstraction reactions by the Evans-Polanyi equation,⁷⁵

$$E_a = \alpha \Delta H^0 + C \quad 11.7$$

where α and C are constants which will be different for each attacking radical. From equation 11.7 it follows that,

$$E_a^{\text{PhOH}} - E_a^{\text{ArOH}} \propto \Delta \Delta H^0 \quad 11.8$$

Recently, there have been several experimental and theoretical studies of the bond dissociation enthalpies (BDE) of substituted phenols in the gas phase, all of which have found that these BDE's yield a LFER with Brown and Okamoto's σ^+ parameter.^{70,76-80}

$$\Delta \Delta H^0 = \text{BDE}(\text{PhOH}) - \text{BDE}(\text{ArOH}) = \Delta \text{BDE} \propto \sigma^+ \quad 11.9$$

There is no hydrogen bonding of phenols to the gas phase and there is no hydrogen bonding of phenols to saturated hydrocarbons. The equations presented above therefore suggest that $\log k_{\text{ArOH/Y}\cdot}^o$ for hydrogen atom abstractions from phenols in the gas phase and in saturated hydrocarbons, should both be related to σ^+ , i.e.,

$$\log k_{\text{ArOH/Y}\cdot}^o \propto \sigma^+ = \rho^+ \sigma^+ + b \quad 11.10$$

This relationship should be valid in non-hydrogen bond accepting solvents for the reactions of meta- and para-substituted phenols (and possibly ortho-methyl-substituted phenols, *vide infra*) provided the Evans-Polanyi equation holds true.

For the reactions of phenols with DPPH• the line represented by equation 11.10 will be defined using two rate constants for the DPPH• reaction with two different phenols in heptane. One will be for 4-methoxyphenol which will be predicted from its measured value in DMSO. The other will be for 4- α,α,α -trifluorocresol which will be measured in heptane. These phenols were chosen because they afford a reasonably large range in σ^+ and because both are soluble in heptane. The reliability of the line constructed according to equation 11.10 from these two kinetic results will be tested by measuring rate constants for several other phenols and comparing these values with the predicted values.

The substituted phenols chosen to compare predicted rate constants with experimental values were: vitamin E, phenol, 4-methoxyphenol, 2,4,6-trimethylphenol, 4-*tert*-butylphenol, 4-chlorophenol, 3-chlorophenol, and 3,5-dichlorophenol. DPPH• was chosen as the hydrogen atom abstractor because its reaction with phenols is endothermic and relatively slow, so that the kinetics would not be limited by diffusion. In addition, the DPPH• radical has a relatively strong adsorption at ~ 520 nm making the kinetics easy to monitor with a standard spectrophotometer.

11.2 Experiments and Results

The rates for the H-atom abstraction from the phenols were measured after rapidly mixing stock heptane solutions of the phenol and DPPH• at 298 K, in a quartz cell having a 1 cm path length. Since the reaction is endothermic and known to be reversible, the experimental conditions were chosen to avoid (or minimize) any interference from the back reaction. The kinetics were obtained by monitoring the decay of the absorption due

to the DPPH• radical at its band maximum, 510 nm in n-heptane, relative to the isosbestic point at 422 nm, using a Hewlett Packard Diode Array spectrophotometer, model 8452A, equipped with a HP 89090A programmable block heater.

It should be noted that the band maximum and the isosbestic point are solvent dependent, e.g., for the DPPH•/4-methoxyphenol reaction in DMSO the band maximum is observed at 526 nm isosbestic point at 440 nm, Figure 11.1, whereas in heptane for the same reaction the band maximum and isosbestic are at 510 and 422 nm respectively.

The reaction times were generally between 120-3000 seconds. To allow for base line drift the isosbestic kinetic trace was subtracted from the decay kinetic trace to give a corrected kinetic trace, Figure 11.2. The reaction times were generally between 120-3000 seconds. To allow for base line drift the isosbestic kinetic trace was subtracted from the decay kinetic trace to give a corrected kinetic trace, Figure 11.2. The experimental pseudo-first order rate constant, k_{exptl} , is obtained from the kinetic data and equation 11.11.

$$\left(\frac{A - A_{\infty}}{A_o - A_{\infty}} \right) = \exp(-k_{exptl} \cdot t) \quad 11.11$$

Values of k_{exptl} were determined using at least 5 different phenol concentrations and were then plotted against the phenol concentration. Straight lines were obtained (generally $r^2 \geq 0.98$) the slopes of which yield the second-order bimolecular rate constants. The measured bimolecular rate constants for hydrogen atom abstraction by DPPH• from 4-methoxyphenol in DMSO and from 4- α,α,α -trifluorocresol in heptane are reported in Table 11.1.

Figure 11.1. Two isosbestic points observed using a UV/Vis-spectrophotometer during the DPPH• / 4-methoxyphenol reaction in dimethylsulfoxide.

Figure 11.2. Decay of DPPH radicals reacted with α,α,α -trifluorocresol, in n-heptane at 298K monitored at $\lambda_{\max}$ 510 nm (a). The isosbestic point (b) was monitored at 422 nm. The decay corrected for any baseline drift is shown (c).

Table 11.1. Rate Constants for Hydrogen Atom Abstraction by DPPH• from 4-methoxyphenol and 4- α,α,α -trifluorocresol in DMSO and heptane, respectively, at 298 K.

	Phenol	Solvent	[DPPH] (M) ^a	[Phenol] (M) ^b	k/ (M ⁻¹ s ⁻¹)	σ^+
3	4-methoxyphenol	DMSO	4.75×10^{-5}	0.315	0.047 ₈	-0.78
7	4- α,α,α -trifluoro- cresol	heptane	2.60×10^{-5}	0.197	0.044 ₀	0.61

^a Concentration of DPPH used to measure the rate constant. ^b Highest concentration of phenol used.

The rate constant for H-atom abstraction from 4-methoxyphenol by DPPH• in heptane was calculated as follows: $\alpha_2^H = 0.55_0$ and thus,

$$M_{4-MeO} = -8.3_2 \times 0.55_0 = -4.5_8 \quad 11.12$$

$\beta_2^H = 0.78$ for DMSO and $\log(k_{4-MeO/DPPH\bullet}^{DMSO}) = -1.32$. The rate constant in heptane is therefore given by,

$$\log k_{4-MeO/DPPH\bullet}^o = \log k_{4-MeO/DPPH\bullet}^{DMSO} + 4.5_8 \times 0.78_0 \quad 11.13$$

so,

$$\log k_{4-MeO/DPPH\bullet}^o = -1.3_2 + 4.5_8 \times 0.78_0 = 2.2_0 \quad 11.14$$

With the rate constant calculated in equation 11.14 and the one measured for 4- α,α,α -trifluorocresol in heptane a Hammett type plot was constructed in the form of

$\log k_{ArOH/DPPH\bullet}^o$ versus σ^+ as shown in Figure 11.3. The equation of the line in this figure is,

$$\log k_{ArOH/DPPH\bullet}^o = 0.21_5 - 2.5_8 \Sigma \sigma^+ \quad 11.15$$

From this equation, rate constants have been predicted for eight phenol / DPPH $\cdot$ reactions in heptane from their σ^+ parameters. The predicted and experimental values are reported in Table 11.2.

Figure 11.3. Line of equation 11.15 as determined from the predicted rate constant for 4-methoxyphenol(●) and DPPH in heptane and, the measured rate constant for the reaction 4- α,α,α -trifluorocresol (■) and DPPH in heptane.

Table 11.2. Predicted (from equation 11.15) and measured bimolecular rate constants for hydrogen atom abstraction from various substituted phenols by 1,1-diphenyl-2-picrylhydrazyl (DPPH[•]) in n-heptane at 298 K.

	Phenol	$\Sigma\sigma^+$	[DPPH] ^a (M)	[Phenol] ^b (M)	k /M ⁻¹ s ⁻¹ Predicted	k /M ⁻¹ s ⁻¹ Measured
1	α -tocopherol	-1.40 ^d	–	–	6620	7400 ^c
2	2,4,6-trimethyl-phenol	-0.72 ^d	3.44 x 10 ⁻⁵	8.48 x 10 ⁻⁴	117	41.9
3	4-methoxyphenol	-0.78	1.23 x 10 ⁻⁵	9.21 x 10 ⁻⁴	167	240
4	4-t-butylphenol	-0.26	2.23 x 10 ⁻⁵	2.04 x 10 ⁻²	7.67	3.1
5	phenol	0.0	–	–	1.64	0.160 ^c
6	4-chlorophenol	0.11	2.46 x 10 ⁻⁵	6.99 x 10 ⁻²	0.855	1.11
8	3,5-dichlorophenol	0.74	4.65 x 10 ⁻⁴	0.140	0.0204	0.037
12	3-chlorophenol	0.37	1.76 x 10 ⁻⁵	0.180	0.183	0.151

^a Concentration of DPPH used to measure the rate constant. ^b Highest concentration of phenol used. ^c Gathered from the literature⁵⁷ and measured in octane. ^d Calculated using the relation found by M. Jonsson *et al*, $\sigma_o^+ = 0.66\sigma_p^+$.⁷⁰

11.3 Discussion

The measured rate constants for eight phenol / DPPH[•] reactions reported in Table 11.2 have been plotted against $\Sigma\sigma^+$ in Figure 11.4. Although the line has been drawn through the kinetic data points for 4-methoxyphenol and 4- α,α,α -trifluorocresol, the measured values for the other eight phenols fall fairly close to this line. These results are particularly dramatic when it's remembered that the rate constant for 4-methoxyphenol was measured in DMSO and its value in heptane (which differs by a factor of 3500 from that in DMSO) was predicted using the appropriate α_2^H and β_2^H values. This extrapolated rate constant and the value measured for 4- α,α,α -trifluorocresol in heptane were then used to predict the rate constants for eight other phenols in heptane.

Figure 11.4. LFER of $\log(k^\circ_{\text{ArOH/DPPH}\cdot})$ against $\Sigma\sigma^+$. The line has been fitted only to the measured value for 4- α,α,α -trifluorocresol(■) and the calculated rate constant for 4-methoxyphenol (●). The open circles represent experimental data, the numbers correspond to entries in Table 11.2.

It should also be noted that equation 11.2 was determined from alkoxyl radical data and was applied here to predict M_{4-MeO} , which quantity was then used to predict the 4-MeO- C_6H_4OH / DPPH• rate constant in heptane. This provides yet another confirmation that KSE's are independent of the attacking radical.

Since there are over 200 σ_p^+ and 500 σ_m^+ parameters listed in one review article³⁹ it is possible to predict over 700 rate constants from equation 11.15, and that is only for mono-para or -meta substituted phenols. Considering that the correlation of equation 11.15 has been demonstrated to hold for mono, di, tri, and penta-substituted phenols, the number of possible rate constant predictions grows extremely large. For example, with 3,4,5-trisubstituted phenols the number of rate constants that can be predicted (based on 200 σ_p^+ and 500 σ_m^+ parameters) is,

$$\# \text{ of phenols} \approx 200 \times (500)^2 = 5 \times 10^7$$

That is, for 3,4,5-trisubstituted 50 million rate constants may be predicted for their reactions with DPPH in alkane solvents. In addition, for each phenol rate constants can be predicted in another 250 solvents. Thus, for the reaction of 3,4,5-trisubstituted phenols with DPPH over one hundred billion rate constants may be predicted from parameters, which have already been determined. That is,

$$\begin{aligned} \# \text{ of rate constants} &\approx \\ 5 \times 10^7 \times 250 &= 125\,000\,000\,000 \approx 1 \times 10^{11} \end{aligned}$$

In chapter 10, I found that rate constants for hydrogen atom abstraction from a specific hydrogen atom donor, MXH, in any solvent could be reliably predicted from one absolute rate constant, via equation 11.16

$$\log k_{MXH/Y\bullet}^s = \log k_{MXH/Y\bullet}^o - 8.3_2(\alpha_2^H \times \beta_2^H) \quad 11.16$$

Upon substituting equation 11.15 into 11.16 an expression is obtained that allows rate constants to be predicted for any ArOH / DPPH $\cdot$ reaction without any further measurements being required. This equation is

$$\log k_{ArOH/DPPH\bullet}^s = 0.21_5 - 2.5_8 \Sigma \sigma^+ - 8.3_2 \times (\alpha_2^H \beta_2^H) \quad 11.17$$

and it tells us that by merely supplying the appropriate parameters to describe the hydrogen atom donor (α_2^H), the reactivity of phenol ($\Sigma \sigma^+$), and the hydrogen bond accepting ability of the solvent (β_2^H) hundreds of billions of rate constants may be predicted for the reaction:

Moreover, if the equation which relates $\log(k_{ArOH/DPPH\bullet}^o)$ with $\Sigma \sigma^+$ is known for any other radical, then the appropriate substitution into equation 11.17 allows predictions to be made for that radical without any further measurements.

Equation 11.17 may be expressed in a more general form,

$$\log k_{ArOH/Y\bullet}^s = \rho_{Y\bullet}^+ \Sigma \sigma^+ - 8.3_2(\alpha_2^H \beta_2^H) + b \quad 11.19$$

Equation 11.19 includes a quantity, $\rho_{Y^\bullet}^+$, which is the slope of the $\log k_{\text{ArOH/Y}^\bullet}^0$ vs. $\Sigma\sigma^+$ plot, that describes the reactivity of the attacking radical. Exothermic reactions will have relatively small $\rho_{Y^\bullet}^+$, whereas endothermic reactions have relatively large $\rho_{Y^\bullet}^+$.⁶¹

11.4 Conclusion

Rate constants for radical / phenol reactions can be reliably predicted from the sum of the σ^+ parameters of the substituents on the phenol. This allows rate constants to be predicted for hydrogen atom abstraction from all sterically non-hindered phenols in any solvent provided rate constants are known for two phenols having significantly different $\Sigma\sigma^+$ values. The necessary data are already available for DPPH $\cdot$ (this work), RO $\cdot$ (this work), ROO $\cdot$,⁸¹ and an alkyl radical, PhCMe₂CH₂ $\cdot$.⁵⁸

Table 11.3. Quantities that define equation 11.10 and allow rate constants to be predicted for radical / phenol reactions from $\Sigma\sigma^+$.

Radical	ρ^+	b
DPPH $\cdot$	-2.58	0.22
RO $\cdot$	-0.39	9.3
ROO $\cdot$ ^a	-1.38	4.18
PhCMe ₂ CH ₂ $\cdot$ ^b	-1.06	5.2

^a Values were measured in styrene⁸¹, it was assumed that $\beta_2^H(\text{styrene}) = \beta_2^H(\text{benzene})$ which allowed the rate constants to be predicted in a alkane solvent and the parameters to be determined. ^b Rate constants gathered from the literature⁵⁸ were measured in benzene, the rate constants were predicted in a saturated hydrocarbon solvent and then a plot of $\log k^0/\text{M}^{-1}\text{s}^{-1}$ vs. $\Sigma\sigma^+$ was used to determine ρ^+ and b.

12 Consequences of KSE and Linear Free Energy Relationships

12.1 Introduction

Although LFER involving σ or σ^+ substituents have been extensively employed by chemists studying hydrogen atom abstraction from substituted toluenes, phenols etc.,^{61,81-86}

little attention has been paid to kinetic solvent effects. Scaiano and coworkers measured the absolute rates of hydrogen atom abstraction from para- and meta- substituted phenols by *tert*-butoxyl radicals in 1 : 2 benzene – di-*tert*-butyl peroxide and found a σ^+ LFER.⁸⁷ The reaction constant (ρ^+) was compared to that reported earlier by Ingold in which relative rates were measured in tetrachloromethane.⁸³ The ρ^+ values were slightly different, the difference was suggested to be due to a difference in the reactivity in the *tert*-butoxyl radicals in benzene and a contribution from hydrogen bonding between the solvent and the phenol. However, from other work,^{57,58} and the work presented in this thesis it is now firmly established that that KSE's for phenols are not due to radical / solvent interactions, but are due solely to hydrogen bonding. The purpose of this chapter is to study the effect solvents have on a σ^+ LFER by calculating the rate constants for hydrogen atom abstraction by DPPH $\cdot$ from substituted phenols in several solvents.

12.2 Experimental and Results

The absolute rate constants for DPPH[•] / phenol reactions were predicted using the equation

$$\log k_{ArOH/DPPH\bullet}^s = \log k_{ArOH/DPPH\bullet}^o + M_{ArOH} \times \beta_2^H \quad 12.2$$

where

$$\log k_{ArOH/DPPH\bullet}^o = 0.21_5 - 2.5_8 \times \sigma^+ \quad 12.3$$

and

$$M_{ArOH} = -8.3_2 \times \alpha_2^H \quad 12.4$$

The rate constants were calculated for the phenols listed in Table 12.1. These phenols were chosen because they provide a substantial range in their σ^+ values. The rate constants were calculated in the following solvents: alkane, benzene, anisole, pyridine and HMPA. The results are reported in Table 12.1 together with the β_2^H values of the solvents, and the α_2^H and $\Sigma\sigma^+$ values of the phenols.

Table 12.1. Calculated rate constants for hydrogen atom abstraction from selected phenols by DPPH[•] radicals at 298 K.

$\beta_2^H =$		0	0.14	0.26	0.62	1.00
		alkane	benzene	anisole	pyridine	HMPA
Phenol ^a		$\log(\frac{k}{M^{-1}s^{-1}})$				
1	(0.370) vitamin E (-1.4) ^b	3.83	3.40	3.03	1.92	0.75
2	(0.374) 2,4,6-trimethylphenol (-0.72) ^b	2.07	1.64	1.26	0.14	-1.04
3	(0.550) 4-methoxyphenol (-0.78)	2.23	1.54	0.95	-0.82	-2.68
4	(0.571) 4-tert-butylphenol (-0.26)	0.89	0.22	-0.35	-2.06	-3.86
5	(0.590) phenol (0.0)	0.22	-0.47	-1.06	-2.83	-4.69
6	(0.670) 4-chlorophenol (0.11)	-0.07	-0.85	-1.52	-3.52	-5.64
7	(0.683) 4-(CF ₃)-phenol (0.61)	-1.36	-2.15	-2.84	-4.88	-7.04
13	(0.569) 4-methylphenol (-0.31)	1.01	0.35	-0.22	-1.92	-3.72
14	(0.629) 4-fluorophenol (-0.07)	0.40	-0.34	-0.97	-2.85	-4.84
15	(0.674) 4-bromophenol (0.15)	-0.17	-0.96	-1.63	-3.65	-5.78
16	(0.787) 4-cyanophenol (0.66)	-1.49	-2.40	-3.19	-5.55	-8.04
17	(0.824) 4-nitrophenol (0.79)	-1.82	-2.78	-3.61	-6.07	-8.68
18	(0.595) 4-phenylphenol (-0.18)	0.68	-0.01	-0.61	-2.39	-4.27
19	(0.519) 2-methylphenol (-0.21)	0.75	0.14	-0.37	-1.93	-3.57
20	(0.390) 2,6-dimethylphenol (-.41) ^b	1.28	0.83	0.44	-0.73	-1.96
21	(0.428) 4-Me ₂ N-phenol (-1.7)	4.60	3.92	3.34	1.59	-0.25

^a The number in parenthesis in front of the phenol is the α_2^H -value, and the number following the phenol is its $\Sigma\sigma^+$ constant. ^b Calculated using the relationship found by M. Jonsson, *et al.*,⁷⁰ $\sigma_0^+ = 0.66\sigma_p^+$.

Figure 12.1. A plot of calculated $\log(k^S_{\text{ArOH/DPPH}\cdot})$ vs. the β_2^H solvent parameter (a). A plot of calculated $\log(k^S_{\text{ArOH/DPPH}\cdot})$ vs. $\Sigma\sigma^+$ in several solvents, (o) $\beta_2^H = 0.0$, (■) $\beta_2^H = 0.14$, (□) $\beta_2^H = 0.26$, (x) $\beta_2^H = 0.62$, (+) $\beta_2^H = 1.00$, (b). Numbers correspond to entries in Table 12.1.

Figure 12.2. Hammett type plot of $\log k^s_{\text{ArOH/DPPH}} / \text{M}^{-1} \text{s}^{-1}$ against $\Sigma\sigma^+$ for the phenols in Table 12.1 and the rate constants predicted in alkane (O) solvent and HMPA (+) solvent. Numbers correspond to entries in Table 12.1.

12.3 Discussion

The calculated rate constants for hydrogen atom abstraction from substituted phenols by DPPH[•] are reported in Table 12.1. The data have been plotted in Figure 12.1a as $\log(k^o_{\text{ArOH/DPPH}})$ vs. β_2^H . This figure shows that some lines intersect. I have already demonstrated that the rate constants for hydrogen atom abstraction from sterically non-hindered phenols by DPPH in a saturated hydrocarbon are determined only by the BDE's of the phenols. The fact that some lines intersect indicates that a phenol which has a lower O-H BDE (and is, therefore, more reactive in an alkane) but is a good hydrogen bond donor will be less reactive in basic solvents than a phenol which has a higher O-H BDE but is a poor hydrogen bond donor. For example in an alkane solvent

($\beta_2^H=0.00$) 4-N,N-dimethylaminophenol($\Sigma\sigma^+=-1.7$) is the most reactive phenol studied but in pyridine ($\beta_2^H=0.62$) the dimethylaminophenol is less reactive than α -tocopherol ($\Sigma\sigma^+=-1.4$), see Figure 12.1b and Table 12.1. It is noteworthy that only three phenols produce significant intersections. These three phenols are α -tocopherol, 2,4,6-trimethylphenol, 2,6-dimethylphenol (points 1, 2, 20) in Figure 12.1a. The influence of 2,6-dimethyl substitution on the abilities of phenols to act as hydrogen bond donors is discussed further in appendix A.2.

In Figure 12.1b and 12.2 Hammett type plots have been constructed. The slopes of the lines (ρ^+) increase and the quality of the fit to a straight line decrease as the solvent becomes a better hydrogen bond acceptor, i.e., as β_2^H increases from 0.00 through 0.14, 0.26 and 0.62 to 1.00. For example, in an alkane ($\beta_2^H=0.00$) $\rho^+ = -2.58$ whereas in HMPA ($\beta_2^H=1.00$) $\rho^+ = -4.12$ and $r^2 = 0.93$. As a second example, from the work presented in Chapter 9 on hydrogen atom abstraction from phenols by *tert*-alkoxyl radicals, in alkane solvents, $\rho^+ = -0.39$ but if the measurements had been made in HMPA the ρ^+ value would have been -1.78 . It is commonly assumed that the magnitude of a Hammett ρ value and the kind of ρ (i.e., ρ , ρ^+ , etc.) reflects the sensitivity to, and type of, electronic effects that meta and para substituents exert on a family of reactions. However, it is clear that mechanistic conclusions based on the magnitude of ρ^+ for a family of ArOH / Y^* reactions will be of dubious validity in solvents other than alkanes. This is because the polar effects of the substituents on ArOH , reactivity towards Y^* (i.e., on ArO-H BDE's) will be completely overwhelmed in basic solvents by the effects of substituents on the abilities of the ArOH to form hydrogen bonds with these solvents.

Thus the “rule of thumb” that large ρ^+ (or ρ) values indicate that Y^* is relatively unreactive and that the $ArOH / Y^*$ reactions are rather slow does not hold if the kinetic data measurements were made in a strong HBA solvent, *particularly* if such data are then compared with kinetic data for some analogous reaction in poor HBA solvent.

12.4 Conclusion

The role of KSE's must be well understood and accounted for when seeking a Hammett type LFER. As seen in this Chapter, the sensitivity of rate constants to meta and para substituents may be due more to KSE's than to the reactivity of the reagent. Moreover, a LFER may not be found because of KSE's. For example, the prediction of $k_{ArOH / DPPH\bullet}^o$ from σ^+ values would have failed miserably for the phenols with 2,6-dimethyl substituents if I had attempted to correlate $\log k_{ArOH / DPPH\bullet}^s$ with $\Sigma\sigma^+$ for reactions done in pyridine. The data for these phenols would therefore have been wrongfully dismissed because, as we have seen in Chapter 11, $\log (k_{ArOH / DPPH\bullet}^o)$ correlates perfectly to $\Sigma\sigma^+$ in an alkane solvent.

13 Conclusions

The reaction medium plays an important role in determining the rates of hydrogen atom abstractions by radicals *only* when the labile H-atom is capable of forming a hydrogen bond with a solvent molecule. The KSE model is remarkable for both its simplicity and predictive power. It allows KSE's to be understood in terms of a 1:1 substrate molecule / solvent molecule hydrogen bond.

The model predicted that the rate constant for hydrogen atom abstraction would decrease as the hydrogen bond accepting ability of the solvent was increased. This was shown to hold true for numerous ring-substituted phenols, aniline and *tert*-butyl hydroperoxide. The model also predicted that the magnitude of the KSE would depend only on the ability of the substrate to donate a hydrogen bond. For example, on spanning the entire range of solvent HBA abilities from pentane ($\beta_2^H = 0.00$) to HMPA ($\beta_2^H = 1.00$), the rate constants for hydrogen atom abstraction from the relatively poor hydrogen bond donor, α -tocopherol, will decrease by a factor of 1000 whereas, for the relatively good HBD 3,5-dichlorophenol, the rate constants will decrease by a factor of one million. Finally, the model predicts that the KSE will be independent of the attacking radical, a prediction that has been proven correct on several occasions.

My work has led to the following guidelines for predicting rate constants for hydrogen atom abstractions:

1. The KSE depends solely on the ability of the solvent to accept a hydrogen bond and is directly proportional to the solvent's β_2^H parameter.

$$\log k_{RXH/Y}^S = \log k_{RXH/Y}^o + M_{RXH} \times \beta_2^H$$

2. The magnitude of the KSE (M_{RXH}) depends only on the ability of the substrate to donate a hydrogen bond and is directly proportional to the substrate's α_2^H parameter.

$$M_{RXH} = -8.3_2 \times \alpha_2^H$$

3. Rate constants for hydrogen atom abstraction by radicals from non-sterically hindered phenols in saturated hydrocarbon solvents are dependent on the sum of the σ^+ parameters of the substituents.

$$\log k_{ArOH/Y\cdot}^o = \rho^+ \Sigma \sigma^+ + C$$

13.1 Applications of KSE's

The use of phenols as peroxy and alkoxy radical trapping agents in order to probe mechanisms of metal ion catalyzed hydrocarbon oxidations is dependent on a knowledge of relevant rate constants as described in detail in section 1.3.2. Some other applications of KSE's are briefly presented below:

- (1) KSE's have recently been used to direct reactions down chosen pathways.⁸⁸ For example, *tert*-butoxyl radicals generated from the catalytic decomposition of *tert*-butyl hydroperoxide in the presence of cyclohexane can either abstract a hydrogen atom from the alkane or the hydroperoxide.⁸⁸ In a poor HBD solvent the *tert*-butoxyl radical will preferentially react with the hydroperoxide, i.e., $k_{ROOH/RO\cdot} / k_{RH/RO\cdot} = 200$. However, my work shows that if pyridine was used as the solvent, the rate constant for hydrogen atom abstraction from the hydroperoxide would decrease by over two orders of magnitude and now the alkane would compete effectively with the hydroperoxide for the alkoxy radicals, i.e., $k_{ROOH/RO\cdot} / k_{RH/RO\cdot} = 0.4$. Thus with equal molar concentrations the alkane

and the hydroperoxide both peroxy and alkyl radicals are being generated and since the peroxy radical is *persistent* the conditions for the Ingold-Fischer Persistent Radical Effect are met, cross-coupling of the two radicals occurs and the mixed peroxide is produced.⁸⁹

(2) The oxidation of alkanes by aromatic peracids occurs with high regio, chemo and stereoselectivity.

Although saturated hydrocarbons (RH) are readily oxidized, no reaction takes place with primary and secondary alcohols. This is surprising since the C-H bond(s) on the carbon bearing the OH group of the alcohol are weaker than the C-H bonds in alkanes. The paradox of alcohol inertness and alkane reactivity towards aromatic peracids can be readily understood in terms of KSE's. These reactions have been done using the secondary or primary alcohol as the solvent. Since alcohols are fairly good HBA's, the propagation step of the oxidation chain process is strongly retarded. Thus, the alleged inertness of primary and secondary alcohols towards peracids is a consequence of kinetic solvent effects, although these alcohols are actually more reactive towards the attacking aroylperoxy radical, $\text{ArC(O)OO}\cdot$, than the corresponding alkanes.⁹⁰

(3) Another interesting example of KSE's that has also been investigated by Minisci and coworkers concerns the oxidation of α -methylstyrene by *tert*-butyl hydroperoxide catalyzed by Fe(III) .⁹¹

When the reaction is done in benzene, the major product is **1** which is found together with significant amounts of **2** and **5**. However, if pyridine is added to the reaction mixture, **5** becomes the main product. In benzene, a poor HBA solvent, *tert*-butoxyl radicals react chiefly with the *tert*-butyl hydroperoxide to produce *tert*-butylperoxyl radicals which add to the α -methylstyrene to yield the epoxide, **1**.

In the presence of the strong HBA, pyridine, the *tert*-butoxyl radical / hydroperoxide reaction is retarded and a significant fraction of these radicals add to the α -methylstyrene after which the Ingold-Fischer Persistent Radical effect takes over with the transient carbon-centered radical being trapped by the persistent *tert*-butylperoxyl radical.

The ability to alter product profiles by changing the solvent represents an important achievement in free-radical chemistry. The procedures I have developed for

the prediction of KSE's for hydrogen atom abstractions should provide a new and useful tool for synthetic organic chemists.

13.2 Proton Transfer?

The KSE model for hydrogen atom abstractions by radicals has withstood rigorous and critical examination without any failures (to date) in its predictive abilities. The question therefore becomes: Can an analogous simple KSE model be applied to proton transfer reactions? This proton transfer model is shown below.

Similar assumptions to those made in section 7.2.3. for hydrogen atom transfer would be expected to apply to proton transfer.

The only kinetic data of which we are aware have been reported by Nielsen *et al.*⁹² These workers measured rate constants for the deprotonation of phenol by the anthracene radical anion, $k_{\text{PhOH}/\text{R}^\bullet}^S$, in four solvents, acetonitrile, propylene carbonate, DMF, and DMSO.

Figure 13.1 shows a plot of $\log(k_{\text{PhOH}/\text{R}^\bullet}^S)/\text{M}^{-1} \text{s}^{-1}$ vs. β_2^H for those four solvents. (The β_2^H for propylene carbonate has not been reported by Abraham. However, I was able to

calculate it from equilibrium constants provided by Nielsen. see Appendix A.7). The straight line in figure 13.1 has been drawn *with the same slope as found for hydrogen atom abstraction from phenol in different solvents*. That is the slope of the line in Figure 13.1, $M_{\text{PhOH/R}^-} = -5.2$ (see Chapters 8.1 and 9.2). It is obvious that Nielsen's proton transfer data are rather well correlated by an M value derived from atom transfer reactions. I conclude that the same rules which govern KSE's for hydrogen atom transfer, are also very likely to govern KSE's for proton transfer.

Figure 13.1. The log of the rate constant for proton transfer from phenol to anthracene radical anion⁹² against the solvent β_2^H value.

13.3 Final Remarks

Rate constants for elementary free radical reactions in homogenous solutions have been measured for over 50 years. There is now an immense wealth of compiled kinetic data for such reactions in all sorts of solvents. (Lanolt-Börnstein, New Series, “Radical Reaction Rates in Solution Vols. 13 and 18, 1994, over 6000 pages of tabulated data) Probably more than half of these kinetic results deals with hydrogen atom abstraction reactions. However, although this immense body of information is neatly tabulated, it must be considered “disorganized”. It is disorganized in the sense that there is no all encompassing rationalization of the data. Thus, it is not obvious why some reactions are subject to kinetic solvent effects while others are not; it is not obvious why the magnitude of the kinetic solvent effects for a related family of reactions are not identical; and it is not obvious why kinetic solvent effects are related to the hydrogen bond donating ability of the substrate and hydrogen bond accepting ability of the solvent. My work provides a simple, *quantitative* explanation for a host of experimental observations on hydrogen atom transfer kinetics and apparently my work can also be used to rationalize proton transfer kinetics.

14 Appendices

14.1 Appendix A.1.

Solvent Cage Effect

Table A.1. In-cage combination of *tert*-butoxyl radicals from di-*tert*-butyl hyponitrite at 45°C in various solvents. Data are from Kiefer and Traylor.⁶⁸

SOLVENT	Viscosity (cp)	Fraction of cage collapse
n-pentane	0.20	0.037
n-hexane	0.250	0.036
n-heptane	0.326	0.084
isooctane	0.379	0.098
n-octadecane	2.774	0.30
20% Nujol	0.613	0.16
40% Nujol	1.14	0.21
60% Nujol	2.76	0.30
70%Nujol	4.70	0.36
80% Nujol	8.74	0.46
90% Nujol	21.7	0.56
100% Nujol	79.9	0.68

Double reciprocal plot of the data in Table A.1 is shown on the next page.

Figure A.1. Double reciprocal plot of the fraction of in-cage product (di-*tert*-butyl peroxide) as a function of reciprocal of absolute viscosity in the decomposition of di-*tert*-butyl hyponitrite.

The line fit to the data is

$$\frac{1}{\text{Cage}} = 1.48 + \frac{6.05}{\eta} - \frac{2.05}{\eta^2} + \frac{0.371}{\eta^3}$$

14.2 Appendix A.2.

A comparison of the pK_a 's of different phenols and their abilities to act as hydrogen bond donors.

Table A.2. Table of data used to construct the graph in Figure A.2.

	Phenol	α_2^H	$\Sigma\sigma^-^c$
1	Vitamin-E	0.370 ^a	-0.83 ^d
2	2,4,6-trimethylphenol	0.374 ^b	-0.40 ^d
3	4-methoxyphenol	0.550 ^a	-0.26
4	4-tert-butylphenol	0.571 ^a	-0.13
5	phenol	0.590 ^a	0
6	4-chlorophenol	0.670 ^b	0.19
7	4- α,α,α -trifluorocresol	0.680 ^a	0.65
8	3,5-dichlorophenol	0.728 ^a	0.74
15	4-methylphenol	0.569 ^b	-0.17
18	4-fluorophenol	0.629 ^b	-0.03
20	4-cyanophenol	0.787 ^b	1.00

^a Values measured in the present work. ^b Quantities gathered from the literature. ⁵² ^c Reference ⁴³. ^d Estimated using the empirical relationship discovered by Jonsson. ⁷⁰

Figure A.2. Plot of Abraham's acidity parameter against $\Sigma\sigma^-$. Data for vitamin-E (1) and 2,4,6-trimethylphenol (2) are represented by ■.

The straight line drawn in figure A.2 correlates only the data for meta and para substituted phenols and has a correlation coefficient of 93%. If the data for vitamin-E and 2,4,6-trimethylphenol are included the correlation drops to 85%. The failure of the correlation of α_2^H with $\Sigma\sigma^-$ (i.e., pK_a) for 2,6-dimethyl substituted phenols can be understood in terms of the different effects these two methyl groups have on the pK_a and on the ability of the phenol to form a hydrogen bond with a base, $:B$.

Scheme A.2

The effect of the two ortho-methyl groups on the ionization of the phenol is purely inductive, with perhaps a small contribution from van der Waals interactions, but the equilibrium constant for hydrogen bonding is also subject to steric effects as suggested by Barclay.⁵⁹ The preferred geometry of an intermolecular hydrogen bond is linear, but this linear geometry will be distorted by one of the ortho-methyl groups. This distortion causes a decrease in the enthalpy of hydrogen bond formation with :B and hence a decrease in the equilibrium constant for hydrogen bond formation. Thus KSE's for 2,6-dimethyl substituted phenols are much better reflected by their α_2^H values than by the $\Sigma\sigma^-$ values.

14.3 Appendix A.3.

Data used to determine $M_{t-BuOOH}$. Kinetic data were gathered from the literature.⁵⁴

Table A.3 Measured absolute second order rate constants in various solvents, at 298 ± 2 K, for the reaction of *tert*-butyl hydroperoxide with cumyloxyl radicals.

Solvent		$10^{-7} k_{t-BuOOH / RO\bullet}$ ($M^{-1}s^{-1}$)	$\hat{a}_H^2$
II	tetrachloromethane	25.0	0.05
III	chlorobenzene	16.0	0.09
IV	benzene	13.0	0.14
V	anisole	4.70	0.26
VII	methyl acetate	0.990	0.40
VIII	acetic acid	1.60	0.42
XIII	benzonitrile	1.71	0.42
IX	acetonitrile	0.870	0.44
X	ethyl acetate	1.05	0.45
XIV	γ -valerolactone	0.759	0.47
XII	<i>tert</i> -butanol	0.670	0.49

Figure A.3. Plot of $\log(k_{t-BuOOH/RO\cdot}^S)$ vs. β_2^H . The slope of the line is -3.52 .

14.4 Appendix A.4.

Kinetic data used to determine M_{ArNH_2} . Rate constants were gathered from the literature.⁵⁵

Table A.4. Measured absolute second order rate constants in various solvents, at 298 ± 2 K, for the reaction of aniline with cumyloxyl radicals.

	Solvent	$110^{-8} k_{PhNH_2/RO\bullet}$ ($M^{-1}s^{-1}$)	β_2^H ^a
II	tetrachloromethane	4.7	0.05
III	chlorobenzene	3.6	0.09
IV	benzene	2.8	0.14
V	anisole	1.5	0.26
VI	methyl formate	0.82	0.38
VII	methyl acetate	0.97	0.40
VIII	acetic acid	0.53	0.42
IX	acetonitrile	0.66	0.44

Figure A.4. Plot of $\log(k^S_{PhNH_2/RO\bullet})$ vs. β_2^H . The slope of the line is -2.22 .

14.5 Appendix A.5.

Kinetic data used to determine $M_{2-\text{MeOPhOH}}$. Data were gathered from the literature.⁷¹

Table A.5. Measured absolute second order rate constants in various solvents, at 298 ± 2 K, for the reaction of 2-methoxyphenol with cumyloxyl radicals.

Solvent		$10^{-7} k_{2-\text{MeOPhOH} / \text{RO}\cdot}^S$ ($\text{M}^{-1}\text{s}^{-1}$)	β_2^H
IB	pentane	11	0.00
II	tetrachloromethane	9.3	0.05
IV	benzene	8.2	0.14
V	anisole	3.7	0.26
IX	acetonitrile	1.6	0.44
X	ethyl acetate	1.5	0.45
XII	tert-butanol	1.3	0.49

Figure A.5. Plot of $\log(k_{2-\text{MeOPhOH} / \text{RO}\cdot}^S)$ vs. β_2^H . The slope of the line is -1.98 .

14.6 Appendix A.6.

Data and graph used to determine ρ^+ for the hydrogen abstraction by *tert*-alkoxyl radicals from phenols in alkane solvent.

Figure A.6. Hammett type plot of $\log(k^{\circ}_{ArOH/RO\cdot})/M^{-1}s^{-1}$ against $\Sigma\sigma^+$. The data is given in Table 9.7.

14.7 Appendix A.7

Table A.7. Data used to construct graph in Chapter 13.

Solvent	$K_{\text{PhOH}}^S (\text{M}^{-1})^b$	$\hat{a}_2^H$ (literature) ^a	$\hat{a}_2^H$ (calculated) ^c	$k_{\text{PhOH/R}}^S$ ($\text{M}^{-1}\text{s}^{-1}$) ^a
MeCN	5.1	0.44	0.41	2.81×10^5
propylene carbonate	9.2	n.a.	0.47	1.26×10^5
DMF	75	0.66	0.68	5.77×10^3
DMSO	210	0.78	0.78	3.41×10^3

^a Obtained from the literature.⁹² ^b Values gathered from the literature.⁵³ ^c See text.

The calculated $\hat{a}_2^H$ values are based on equilibrium constants provided by Neilsen.⁹² Phenol is a calibrated HBD which allows the $\hat{a}_2^H$ value for a HBA to be calculated from equilibrium constants:

$$\log K_B^H = \frac{(\log K_{\text{PhOH}}^S D_A)}{L_A},$$

For phenol, $L_A = 0.946$, and $D_A = -0.057$, and

$$\hat{a}_2^H = \frac{(\log K_B^H + 1.1)}{4.636}.$$

It is noteworthy that these equilibrium constants were measured using the HBA as the solvent, whereas Abraham's values were measured using dilute solutions of the HBA and HBD in tetrachloromethane. The excellent agreement between the literature and

predicted values indicate that the surrounding solvent molecules have little affect on equilibrium constants (and hence on β_2^H values) as first suggested Neilson.

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